Basu *et al.*
Biotechnology for Sustainable Materials (2025) 2:4
https://doi.org/10.1186/s44316-025-00027-0

Biotechnology for Sustainable Materials

REVIEW

Open Access

Modified thiomer-based nanomedicines in management of ocular complications: a review

Biswajit Basu[1*], Suraj Mallick[1], Suman Dhauria[1], Anisha Das[1] and Sudarshan Singh[2,3*]

Abstract

Thiomer-based nanomedicines provide a diverse approach to delivering ophthalmic drugs and controlling problems. The review digs into the development, characterization, and use of thiomer and modified thiomer-based nanomedicines. It emphasizes their biocompatibility, which ensures that they are safe to use in the body. It also emphasizes their mucoadhesive characteristics, which assist the drug stick to the mucosal surfaces of the eye, therefore increasing efficacy. The study also emphasizes the possibility of higher medication bioavailability, which means that more of the medicine will reach and influence the target region of the eye. This holistic strategy is intended to improve eye treatment outcomes. It examines the anatomy of the eye, the categorization of ocular diseases, and the challenges faced by existing drug delivery techniques. The review centres on the advancement and therapeutic potential of thiomer-based nanomedicines for the treatment of various eye conditions, such as glaucoma, diabetic retinopathy, and age-related macular degeneration. It describes the steps involved in developing and evaluating these nanomedicines, with a focus on their safety and efficacy as determined by toxicological, preclinical, and clinical assessments. Furthermore, the paper covers the regulatory requirements for the approval and use of these novel therapies. Future opportunities for thiomer-based nanomedicines are discussed, as well as potential problems such as manufacturing scalability and assuring consistent treatment effects. The goal is to improve the delivery and efficacy of medicines for these critical eye disorders, therefore enhancing patient care and quality of life.

Keywords Thiomer, Nanomedicine, Ophthalmic drug delivery, Ocular diseases, Therapeutic potential

Introduction

Ocular disorders directly affect human's vision and standard of living. According to a survey performed within 39 countries, 285 million individuals are visually impaired, 82% of blind patients are over 50, with 65% being over age of 50 [1]. Major progress has been assembled in our understanding of ocular pathogenic mechanisms and disorder therapy. However, on behalf of the unique physiological barriers and anatomical characteristics of the human eye, diagnosis and treatment of these complication may be inefficient and lacking precision. Rarely can the present treatment approaches identify serious eye illnesses early on or fully restore vision loss [2]. As a result, great focus is being paid to the development of better eye illness diagnoses and treatments. The aetiology of vision loss is complex, and the main disorders that contribute to this widespread problem include diabetic retinopathy (DR), cataracts, glaucoma, age-related

*Correspondence:
Biswajit Basu
bbasu.pharma@gmail.com
Sudarshan Singh
sudarshansingh83@hotmail.com
[1] Department of Pharmaceutical Technology, School of Health and Medical Sciences, Adamas University, Barasat, Kolkata, West Bengal 700126, India
[2] Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand
[3] Office of Research Administration, Chiang Mai University, Chiang Mai 50200, Thailand

macular degeneration (AMD), and retinal vein occlusion [3]. Complete blindness may result from these conditions if proper therapy is not received. Pharmaceutical companies have made great progress in developing a range of preventative, therapeutic, and rehabilitation strategies that have improved the efficacy of authorised interventions for eye disorders; however, these strategies are rarely enough to totally eradicate these conditions.

Nanomedicine is a form of sustainable nanotechnology to the realm of medicine [4]. It takes use of the dynamic physical, chemical, and biological properties of materials at the nanoscale as opposed to those at the macro or nano-scale. Nanomedicine has the potential to significantly improve sickness prevention, early and accurate diagnosis, and treatment in the next decades. Moreover, the nanomedicine has the ability to improve medication penetration across ocular barriers, boost hydrophobic drug solubility in aqueous solution, and even target tissues and cells. A diversity of nanomedicines, such as liposomes [5–8], polymeric nanoparticles (NPs) [9–12], micelles [13], and dendrimers [14], have been formulated to transport pharmaceuticals into the eye [15] (Fig. 1).

The human eye, a complex and delicate organ, is shielded by numerous barriers to protect the visual axis from infections and inflammations. However, the unique structure of eye create significant obstacles for ocular drug administration's [16]. To get through these barriers, nontechnology based delivery systems, which offer an alternative of conventional drug delivery system required to exhibit features and capabilities, including mucoadhesive [17], protective activity [18], improved solubility [19], tissue or organ targeting [20], permeation [21], uptake enhancing [22], and drug release controlling properties [23]. The origin of polymers into the drug delivery sector has resulted in the development of several innovative delivery methods that can meet the necessary characteristics listed above while having an advantage over other preparations in terms of acceptability and comfort [24]. The most common causes of inadequate absorption, after administration to eye are decreased membrane penetration and enzymatic breakdown. Utilising mucoadhesive polymers may therefore be a useful tactic that has already attracted a lot of attention for improving bioavailability. A mucoadhesive drug delivery system is a system that uses polymers to bind with mucus and deliver drugs to the targeted site [25]. General polymers' mucoadhesive qualities are ineffective, since they only develop a weak, non-covalent connections with the mucosal surface. In several attempts to enhance mucoadhesion, the conjugation of unmodified polymers with thiol groups proved to be a successful strategy. Mucoadhesive polymers with thiol-bearing side chains, known as thiomers, mimic the natural process of mucus glycoprotein formation by creating strong disulphide bonds with the mucin layer. As a result, thiomers can target a wide range of mucosal surfaces, including the gastrointestinal, pulmonary, oropharyngeal, ocular, buccal, nasal, vaginal, and rectal [25]. This review briefly provides the prospective of native and modified thiomers for effective nanomedicine administration. Concurrently, an overview of ocular complications and their related mechanisms, as well as a brief on mechanism and function of thiomers, i.e., improved thiomer characteristics and their treatment in ocular complications have been presented to fulfil the gap in knowledge.

Anatomy of eye and its protection mechanism

The eye, prominent advanced sense organs in the human body, is what gives us our eyesight. The typical human eye has a width of 69 to 85 mm and an axial length of 22 to 27 mm with an estimated total volume of 6.5–7 mL [26]. It possesses distinguishing characteristics, such as its particular anatomy and physiology, and serves a specific role. The six muscles that support their mobility hold the human eyeballs in place as they are situated in the eye socket in pairs. Anatomically, the eye is branched into anterior and posterior segments, which respectively include one-third and two-thirds of the ocular framework. The anterior segment contains the tear, cornea, conjunctiva, anterior and posterior chamber, iris, ciliary body, lens, and aqueous humour whereas the posterior segment includes the sclera, choroid, retina, Bruch's membrane, vitreous humour, optic nerve, and retinal blood vessels. Figure 2 illustrates how the unique architecture of the eye and barrier poses complications for medication delivery.

Barriers of the anterior segment

Tear film barrier

Drug distribution is hampered by the tear film that develops on the surface of the eye, and the effectiveness of medications too due to dilution and drainage through the nasolacrimal system. The tear film composed of three layers: an exterior lipid layer, a middle aqueous layer, and an interior mucous layer. The outer lipid layer prevents water evaporation and hinders medication absorption into the cornea and sclera [27]. However, the mucous layer in the tear film works as a hydrophilic barrier that effectively eliminates germs and debris. Because of the lacrimal turnover rate of 1–3 µL/min [28], causing drug loss from ocular surface to be 500–700 times greater than the drug absorption rate into the anterior chamber [29]. Lacrimation can occur due to irritant medications, specific excipients, and pH changes, which raise tear production to around 300 mL per minute [29]. Over 85% of the medicine

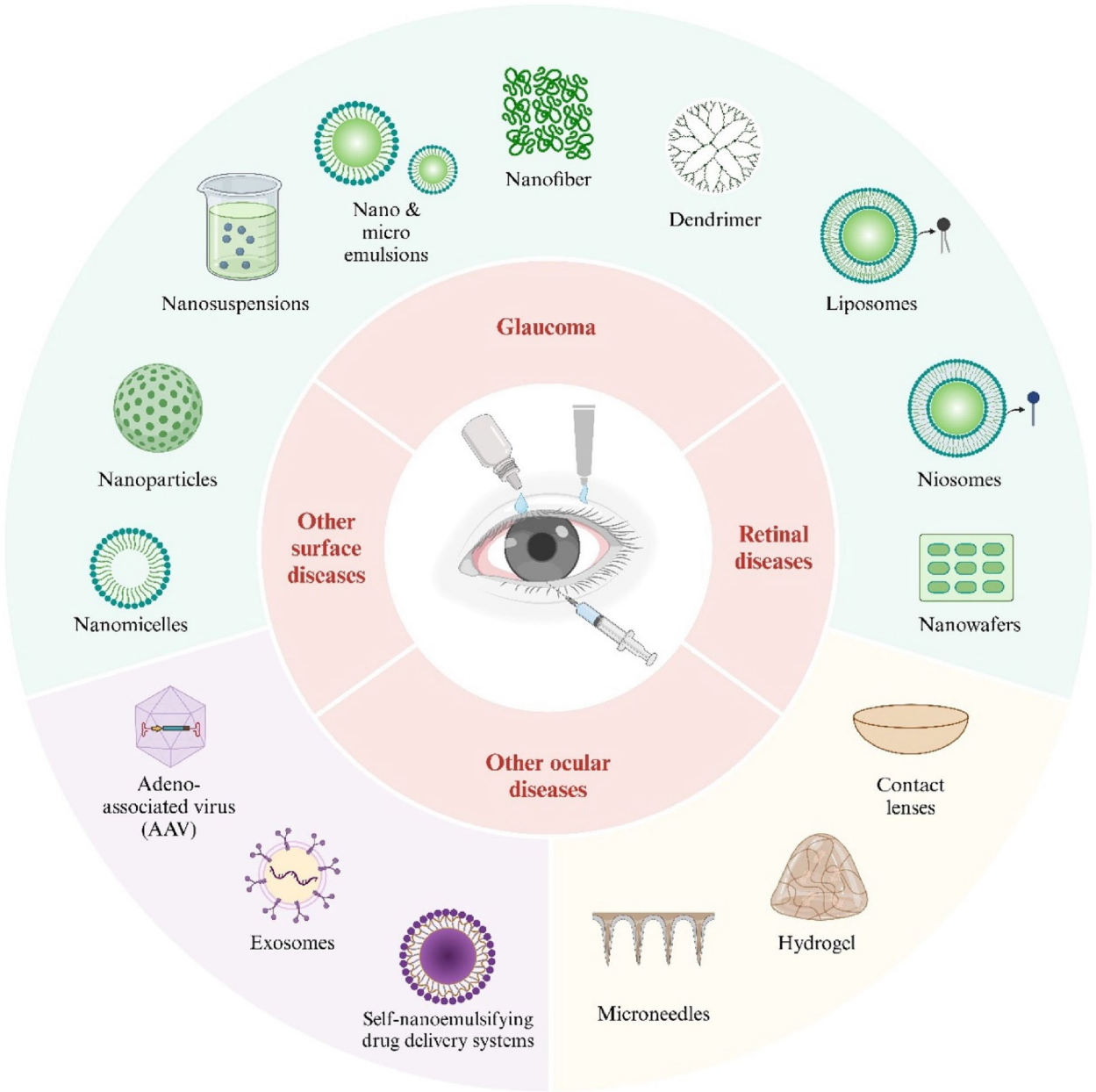

Fig. 1 Diagrammatic representation of various ocular delivery techniques based on nanotechnology

dosage is lost before it reaches the corneal surface as a result of this fast increase, which causes rapid drainage through the nasolacrimal duct. Rapid tear turnover can also cause further dilution of the retained medication, which lowers the diffusion rate and concentration gradient. As a result, intraocular medications demonstrate a low bioavailability in the aqueous humour, which leads in poor drug absorption when applied topically, usually between 0.1% to 5% [30].

Cornea and conjunctival barrier

The cornea, the transparent rearmost layer of the eye's avascular structure, serves an important refractive and barrier function. In addition to two interfaces, the Bowman layer and Descemet's membrane, which is composed of three cell layers: the lipophilic epithelium, the hydrophilic stroma, and the lipophilic endothelium. Whereas the corneal epithelium, consisting of five to seven lipid-rich cell layers with tight junctions and desmosomes,

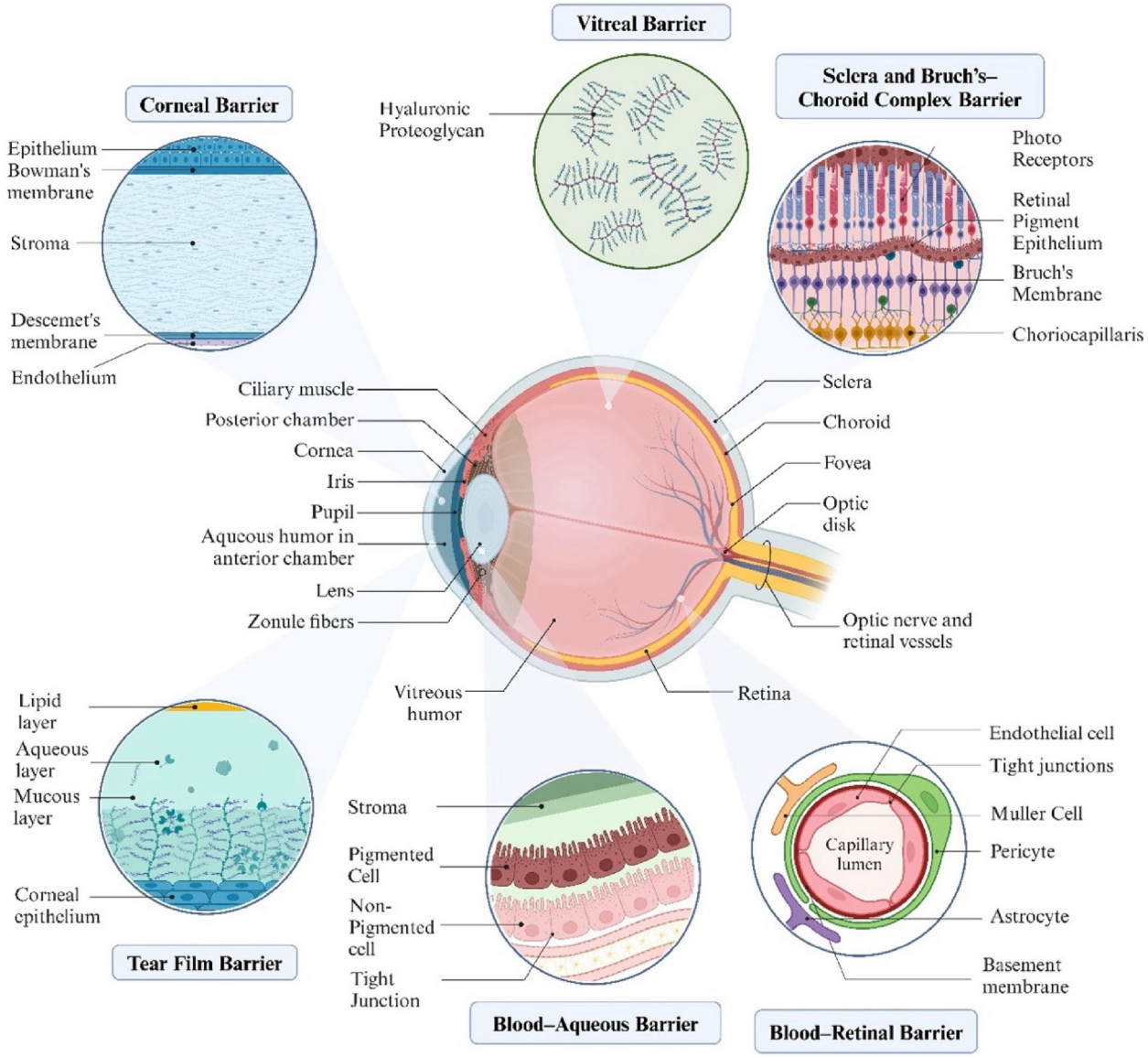

Fig. 2 Diagrammatic model of the ocular anatomy and the physiological barriers to ocular medication

provides a robust barrier that prevents both microbial invasion and medication penetration [29]. In contrast to the cornea, conjunctival capillaries and the lymphatic system limit medicine absorption via conjunctiva, resulting in drug outflow into the circulation and decrease bioavailability. Hydrophilic molecules cannot move passively due to the strong connections of the conjunctival epithelium. Recent study suggests an inverse link between medicine diffuse via the sclera and molecular length [31].

Blood aqueous barrier The blood-aqueous barrier (BAB) is produced by the tight junctions between the inner wall endothelium of Schlemm's canal, endothelial cells in the iris vasculature, and the non-pigmented epithelium of the ciliary process. Paracellular transport governs the flow of ions and other small materials between adjoining cells. Thus, the BAB acts as a specialized doorway for regulated molecular transport rather than being impenetrable [32].

Barriers of the posterior segment

Vitreal barrier

The vitreous is a transparent, gel-like substance that fills the space between the retina and the lens. It is mostly composed of water, hyaluronic acid, collagen types II, IX, V/XI, and other components of the extracellular matrix.The diffusion ability of the vitreal network may be blocked by

positively charged nanomaterials that interact with its negatively charged components, whereas negatively charged particles, such as human serum albumin or polylactic-co-glycolic acid (PLGA), can effectively spread throughout the vitreous humour [33].

Blood-retinal barrier

The two primary barriers that comprise the blood–ocular barrier (BOB) system is the blood–retinal barrier (BRB) and the BAB. Highly selective, the BRB controls the movement of water, proteins, and ions into and out of the retina. The inner BRB (iBRB), which is made up of tight connections between retinal capillary endothelial cells, and the outer BRB (oBRB), which consists of the choroid, Bruch's membrane [34], and retinal pigment epithelium [35], are its two components [36]. The suprachoroid, the layers of big and medium blood vessels, and the choriocapillaris make up the choroid's outermost layer. The choriocapillaris contribute to the elimination of waste from the exterior layers of the retina and the provision of nutrients.

Sclera and bruch's—choroid complex barrier

The choroid, a highly vascularized barrier, separates the retinal pigment epithelium from the sclera. It is composed of five distinct layers, with a thickness of around 200 μm: Bruch's membrane, two vascular layers, the choriocapillaris layer, and the suprachoroidal layer [28]. The choroid repels hydrophilic substances but positively charged lipophilic medicines can adhere to the tissue and create poor-release depots. The shape of a drug's molecules influences how readily it diffuses into the posterior eye segment.

Classification of the ocular disease and associated mechanisms

Ocular diseases are broad pathological conditions of the eyes and structures related to them resulting in loss of vision or vision impairment if left untreated. In general, diseases of the eye may broadly be classified according to the anatomical component affected-thus corneal, retinal, lens, or optic nerve diseases-or classified according to predisposing factors, such as inherited, infectious, inflammatory, degenerative, or traumatic causes. Table 1 providing an overview of common ocular diseases:

Challenges faced during conventional drug delivery in management of ocular complication

Topical, regional, and systemic administration routes are the most common modes of ocular medication delivery. Topical administration includes solutions, gels, ointments, and suspensions, is the most widely recognized and cost-effective technique for treating anterior segment eye problems. However, lacrimation, tear dilution, and tear turnover cause less than 5% of the injected amount to enter the aqueous humor [42]. Regional administration entails injecting the formulation intraocularly or periocularly to reduce systemic adverse effects while improving medication transmission to targeted tissues [43]. Intracameral administration, which includes direct injection into the anterior chamber, is most frequently utilized in cataract surgery for the treatment of anterior segment disorders. Intravitreal injection has been used to treat AMD, diabetic macular edema (DME), retinal vein occlusion (RVO), and endophthalmitis for over 20 years. Although intravitreal injection allows for direct administration of medications to the posterior region, multiple eye punctures may raise the chance of developing problems such as endophthalmitis, hemorrhage, retinal detachment, and patient discomfort [44]. Some other intraocular injection routes include intrastromal, subconjunctival, subretinal, and sub choroidal routes. Other injection techniques in the periorbital route include a wide variety of techniques for local anesthesia of the eye during ophthalmic surgery, including the retrobulbar, peribulbar, posterior juxta scleral, and subtenon injection. Figure 3 demonstrating various methods of ocular injection**.**

Systemic modes of delivery include intravenous and oral routes, such as providing antibiotics for endophthalmitis, carbonic anhydrase inhibitors for intraocular pressure control, and methotrexate and corticosteroids for treating uveitis [44]. Nevertheless, as previously mentioned, BAB and BRB limits access to segments of the eye, thereby limiting bioavailability from systemic administration. This is often higher than what is required for clinical efficacy and can lead to systemic side effects. Apart from this, plasma protein binding, lipophilicity, and distribution clearance are other characteristics that may interfere with accurate therapeutic concentration prediction [46]. Table 2 summarizes several routes of ocular drug delivery and their therapeutic applications, as well as their bioavailability benefits and drawbacks. Figure 4 shows the mechanism of drug metabolism [47].

Thiomer and modified thiomer

Thiolated polymers, commonly known as thiomers, have spawned numerous new areas of polymer-based therapy [52]. Macromolecules exhibiting free thiol groups on their polymer backbone are called thiomers or thiolated polymers. These thiomers can arise when sulfhydryl-bearing compounds are immobilised onto the backbone of well-developed polymeric excipients such chitosan [53–56] and poly(acrylates) [57] as presented in Fig. 5. The development of inter- and intramolecular disulfide bonds imparts strong cohesive qualities to thiomers, resulting to considerably enhanced stability and, as a result, longer disintegration durations and drug release from diverse dosage forms such as tablets,

Table 1 Overview of common ocular diseases its definition, mechanism, factor affecting, sign and symptoms

Ocular Disease	Definition	Mechanism	Factor affecting	Sign and Symptoms	Ref
Cataract	Cataracts, a common lens disorder affecting its transparency, are the primary cause of reversible blindness globally	Oxidative stress leads to protein aggregation, depletion of antioxidants, and dysfunction of Na + /K + ATPase, which causes damage to lens transparency. UV exposure, diabetes, and aging worsen protein misfolding, hydration imbalance, and fiber degeneration, impairing vision	Aging, UV exposure, oxidative stress, diabetes, smoking, alcohol, prolonged steroid use, genetic predisposition, poor nutrition, and systemic diseases like hypertension	Blurred vision, glare, halos, difficulty seeing at night, and fading colors	[37]
Glaucoma	Glaucoma is a progressive optic neuropathy that, regardless of IOP level, is characterized by a particular pattern of visual field abnormalities and a distinctive look of the optic disc	Glaucoma is distinguished by optic nerve injury and progressive vision loss as a result of increasing intraocular pressure caused by inadequate aqueous humor outflow or overproduction	Increased intraocular pressure, age, family history, ethnicity, eye injuries, high blood pressure, diabetes, certain medications, and poor blood circulation to the optic nerve	Progressive vision loss, peripheral vision impairment, eye discomfort, headache, and blurred vision	[38]
Age-related macular degeneration	AMD is a impairment of the retina and choroid that results in a substantial decrease in visual acuity, or sharpness of vision	AMD is defined by the buildup of drusen, retinal pigment epithelium degeneration and choroidal neovascularization, which cause retinal damage, diminished central vision, and gradual loss of visual acuity	Aging, smoking, high-fat diet, genetics, UV light exposure, cardiovascular diseases, and family history	Blurred central vision, difficulty reading, distorted images, and gradual loss of visual acuity	[39]
Diabetic retinopathy	DR is a retinal vascular disease that affects people with diabetes mellitus	DR is caused by extended high blood sugar, which damages the retina's blood vessels, causing leakage, bleeding, ischemia, and neovascularization, thereby impairing vision and potentially leading to blindness	Poor blood sugar control, hypertension, duration of diabetes, high cholesterol, and smoking	Blurry vision, floaters, dark spots, difficulty seeing at night, and eventual vision loss	[40]
Atopic dermatitis (AD)	Chronic inflammatory skin disorder known as AD may manifest with ocular comorbidities like conjunctivitis, atopic keratoconjunctivitis	Ocular AD is characterized by immune dysfunction with elevated IgE and activation of T cells, thereby leading to inflammation, dysfunctional skin barrier, and ocular surface irritation that results in itching, redness, and dryness	Genetics, environmental allergens, immune system dysfunction, skin barrier impairment, and irritant exposure	Itchy, red, swollen eyelids, dry eyes, conjunctivitis, and skin changes around the eyes	[41]
Corneal disorders	Corneal disorders encompass a wide range of conditions such as inflammations, corneal dystrophies, corneal ectasis affecting the cornea, the transparent outer layer of the eye	Keratitis is a common condition characterised by inflammation of the cornea, often caused by infections or injuries, while corneal dystrophies are an inherited conditions that cause progressive changes in the cornea. Conditions like keratoconus involve thinning and bulging of cornea, leading to vision distortion indication of corneal ectasia	This corneal disorders are influenced by a variety of factors, both intrinsic and extrinsic. In addition, environmental factors such as dry and windy conditions can exacerbate conditions like dry eye syndrome	Inflammation, and other associated condition to eye	

Table 1 (continued)

Ocular Disease	Definition	Mechanism	Factor affecting	Sign and Symptoms	Ref
Blepharitis	Blepharitis is a chronic inflammation of eyelids characterized by redness, swelling, and irritations	It typically affects both eyes and is not contagious. The condition often results from clogged oil glands near the eyelashes, leading to symptoms such as itchy, watery, and red eyes, along with crusted eyelashes and sensitivity to light	This is a chronic inflammation of eyelids, is influences by several factors including intrinsic and extrinsic factors. Additionally life style factors such as prolonged contact lense wear, exposure to irritants like dust and chemicals and hormonal changes can increase the risk of developing blepharitis	Itchy, watery, and red eyes, along with crusted eyelashes and sensitivity to light	
Conjunctivitis	Conjunctivitis, commonly known as pink eye, is an inflammation or infection of the conjunctiva, the thin membrane covering the white part of the eye and the inside of the eyelids	The condition can be caused by viral or bacterial infections, allergies, or irritants. Symptoms vary depending on the cause but typically include red or pink eyes, watery or thick discharge, and sensitivity to light	The conjunctivitis is generally not serious and rarely affects vision, but it can be contagious, especially in viral and bacterial forms	It is characterized by redness, itching, and a gritty sensations in the eye	

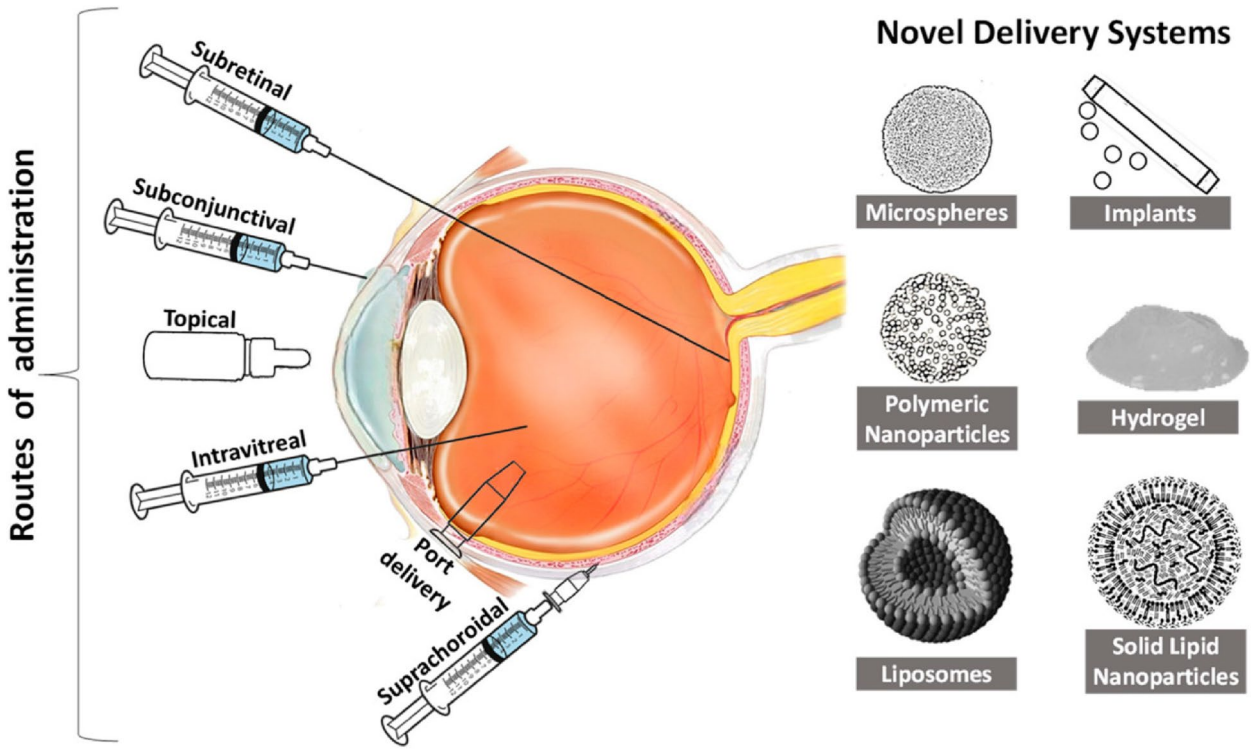

Fig. 3 Illustrations demonstrating various methods of ocular injection. Reproduce with permission from [45] under CCBY 3.0

micro particles, and gels [58].The benefits of thiomers over unmodified polymers include improved mucoadhesion and suppression of enzymes and efflux. Thiolated polymers or native thiomers demonstrate the potential to address a number of significant challenges in the application of macromolecules as therapeutic agents, such as shortcomings in terms of effectiveness, safety, and precise delivery methods [59]. Pros and cons of thiolated polymers is presented in Table 3.

Mechanism of action and its properties

The use of mucoadhesive polymers for better distribution has been regarded as a novel strategy with broad acceptability [25]. Despite their many impressive properties, these systems have drawbacks such as relatively poor mucoadhesion (due to the existence of non-covalent bonds like as hydrogen bonds, Vander Waal's forces, and ionic contacts), which results in modest drug localization at targeted areas [60]. Many improvements have been made since then to the adhesive characteristics. The technique of immobilizing thiol groups onto the unmodified polymer has demonstrated significant improvement in mucoadhesive properties, implying its potential as an efficient excipient for diverse drug delivery systems. These have exceptional mucoadhesion properties due to formation of disulphide bonds with the mucus gel layer, which are comparable to the kind of connections that biological glycoproteins form with the mucosa of the epithelium. Moreover, the oxidation of free thiol groups or thiol/disulfide exchange events between thiomers and cysteine-rich subdomains of the mucin layer result in the formation of disulphide bonds (covalent interactions) [61] (Fig. 6). Table 4 presents a quick comparison of thiolated and non-thiolated systems.

Parameters influencing thiomer properties

Thiol group immobilization

The degree of intra- and inter-disulfide bond formation is strongly linked to in situ thiomer crosslinking. Both the cohesive and adhesive properties are greatly enhanced by this type of crosslinking. Covalent links, also known as disulphide bonds that occur at both inside the polymer and between the polymer and mucus, which may explain these phenomena. Ellman's reagent is applied spectrophotometrically to quantify the thiol content because it has a better selectivity for free thiol groups [60].

Table 2 Summary of routes of administration, applications, benefits, and challenges in ocular delivery

Type	Method	Location	Clinical Use	Benefits	Difficulties	Ref
Systemic	Intravenous/oral	-	Uveitis, optic neuritis, ocular infection, and hypertension	High adherence among patients	Low bioavailability, BOB. Systemic toxicity is caused by excessive doses	[48]
Topical	-	On the cornea's surface	Conjunctivitis, keratitis, uveitis, blepharitis, scleritis, and episcleritis	Excellent patient adherence, self-administration, and non-invasiveness	Efflux pumps, corneal barriers, and tear dilution/turnover	[49]
Intraocular	Intracameral	In the frontal chamber	Endophthalmitis, pupil dilatation, and anaesthesia	Direct distribution to the target site, reduced dose, BRB avoidance, and increased effects	Inadequate patient compliance, The invasiveness of the medications, toxicity, consequences of puncture Haemorrhage, pain, retinal detachment, ocular pressure, and vitreous haemorrhage Endophthalmitis lens cyst development and optic nerve injury	[50]
	Intravitreal	Via the vitreous body	CMV retinitis, AMD, RVO, DME, endophthalmitis, and uveitis			
	Subretinal	Between RPE and neurosensory retina	Cell treatment, DME, and AMD for hereditary retinal dystrophies			
	Intrastromal	Via the stroma of the cornea	Keratitis			
	Suprachoroidal	Between the choroid and the sclera	DME with uveitic macular oedema			
	Subconjunctival	Underneath the conjunctiva	Corneal neovascularisation and keratitis			
Periocular	Posterior juxta sclera	Down to the sclera, posterior to the superotemporal limbus	Triamcinolone for DME and anecortave acetate (Retaane®) for AMD	Selective administration to both anterior and posterior portions, avoiding corneal and conjunctival obstacles, extended. duration of action	Risk of globe rupture or scarring, invasiveness, drug deposition, poor patient compliance, and consequences from punctures (pain, haemorrhage, infection) as well as injury to the nerves and muscles	[51]
	Retrobulbar	Intraconal space	Anaesthesia			
	Peribulbar	Beyond the intramuscular septum of the four rectus muscles	Anaesthesia			
	Sub-tenon	The tenon capsule underneath	Chronic uveitis, macular telangiectasia, anaesthesia			

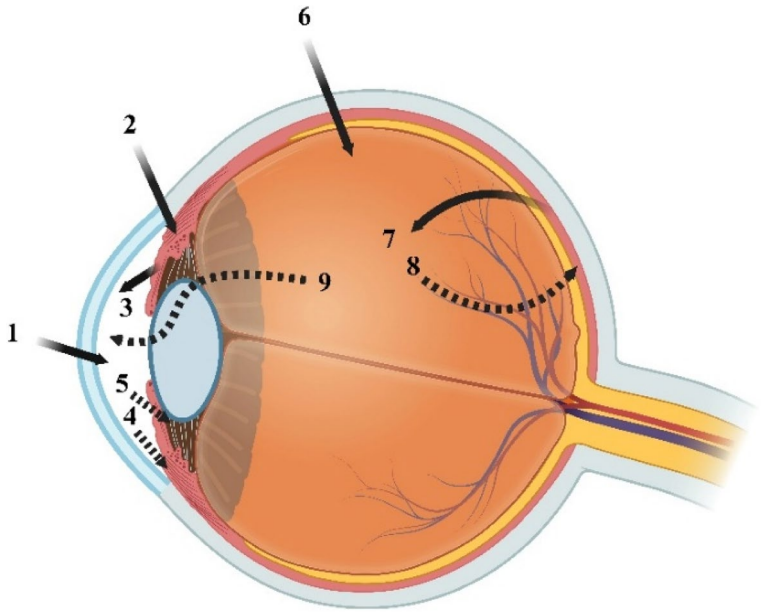

Fig. 4 Diagrammatic representation of ocular pharmacokinetics. Drugs can enter and exit the eye in a number of ways, including drug absorption through tears in the cornea [1], drug absorption through the sclera and conjunctiva [2], drug distribution from the bloodstream to the anterior segment through BAB [3], and drug elimination through the trabecular meshwork and Schlemm's canal [4] and from the aqueous humor across the BAB [5]. Moreover, drugs can be directly injected straight into the vitreous [6] or enter the posterior part of the eye through the BRB [7]. Finally, drugs can be eliminated from the vitreous via both posterior [8] and anterior routes [9]. (Solid arrows: entering route; Dotted arrows: route of elimination)

Swelling index

The thiomers' swelling behaviour significantly affects their stability and adhesion. Swellability is mostly determined by the degree of interdiffusion between the polymer and the mucin layer. Polymers' ability to absorb water is enhanced by thiomerization, which also increases mucoadhesion and stability (cohesive strength). These characteristics, when combined with disulphide bonds demonstrate improvement in viscosity that provide its prolonged presence at mucosal surfaces [62].

pH and ionic character

Ionic strength and pH have no effect on disulphide bonds, yet they are the only factors that impact their formation. The oxidation of free thiol groups at physiological pH serves as the cornerstone of the whole thiomer process, also known as in situ cross linking. At pH 5, free thiol moieties are very susceptible to oxidation. Therefore, thiomer synthesis are performed at a lower pH to avoid or limit the production of undesired disulphide bonds. Furthermore, due to presence of unique cellular structural rearrangement, the presence of cationic charges on the polymer allows for large interaction with the negatively charged mucin, further enhancing mucoadhesion and boosting penetration [63].

Classification

Several drugs have used with thiomers as an appropriate carrier with the goal of activating on different mucosal tissues because of their exceptional qualities. Mucoadhesive polymers including chitosan, polyacrylic acid, polycarbophil, carboxymethyl-cellulose, hydroxymethyl cellulose, and hydroxyethyl cellulose have been modified by immobilizing thiol conjugates such as cysteine, cysteamine, thiourea, and glutathione [64]. The following sections present different classification of thiomers:

Cationic thiomer

Due to their great attraction to negatively charged mucin, cationic polymers are frequently used in mucoadhesion applications. Chitosan's mucoadhesive action is greatly increased in the presence of abundant mucin at neutral or slightly alkaline pH. Because of its advantageous qualities as a mucoadhesive, controlled release, and permeation-enhancing polymer, chitosan has drawn significant attention in pharmaceutical science. Generally, the main amino group on the glucosamine subunits of chitosan is the main target for thiol conjugate immobilisation or anchoring as presented in Fig. 7. When thiol conjugates are inactive, the

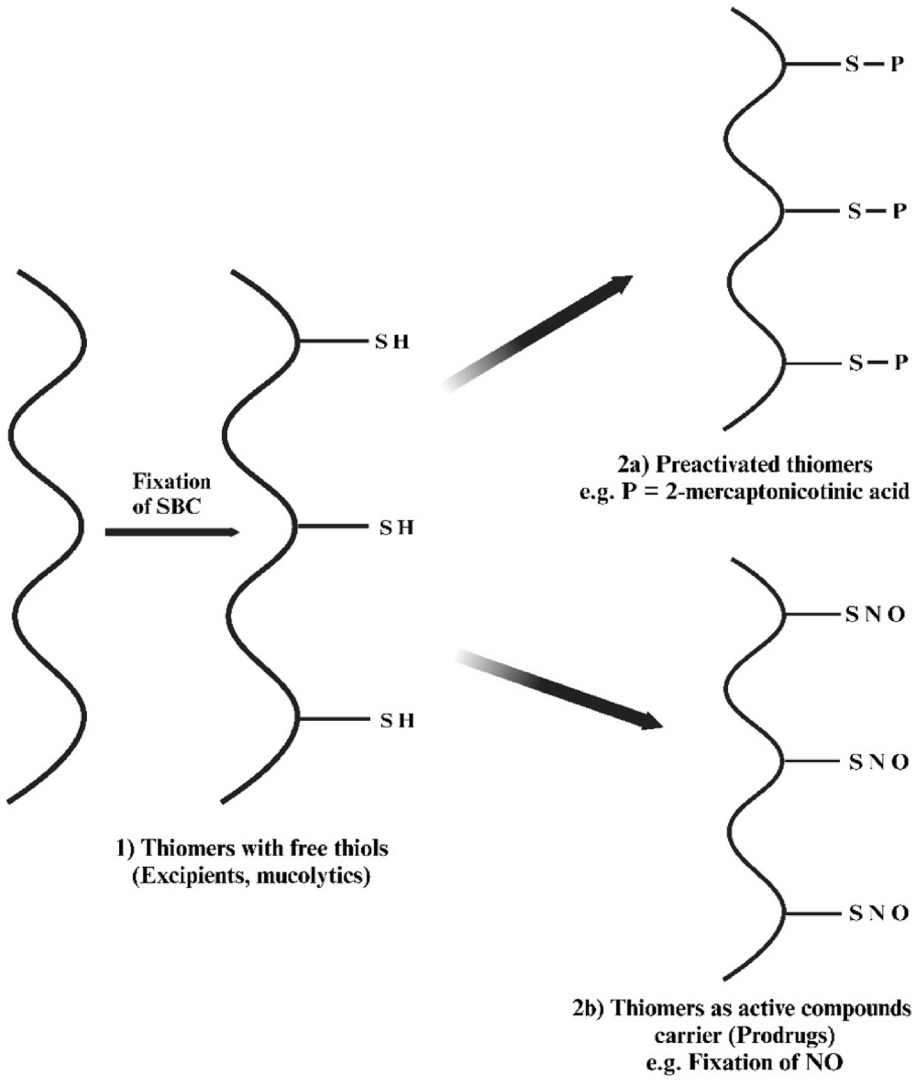

Fig. 5 Thiolated polymers (Thiomers) that may undergo further reactions on the -SH groups delivery

Table 3 Pros and cons of thiolated polymers

Pros	Cons
The formation of disulphide bonds is independent of ionic strength and pH	At higher pH values, the cationic thiomer chitosan exhibits precipitation
Provide a large buffer capacity	Incompatibility with oppositely charged ionic medications
Have exceptional qualities such as mucoadhesion, cohesiveness, and penetration	Unintentional medication release that depends on pH
Provide options for different dose types and administration methods	Ionic repulsion causes poor cross-linking within the thiomer (in case of ionic polymer)

carboxylic group covalently forms amide bonds with the amino group [64]. Moreover, cationic thiomers are often favoured to contain thiol moieties such cysteine, thioglycolic acid, and 4-thio-butyl-amidine [61].

Anionic thiomer

The carboxylic groups of anionic polymers provide a conjugating site for thiol moieties through the production of amide bonds (initiated by carbodiimides) as presented in Fig. 8. Cysteine, homocysteine, and cysteamine are

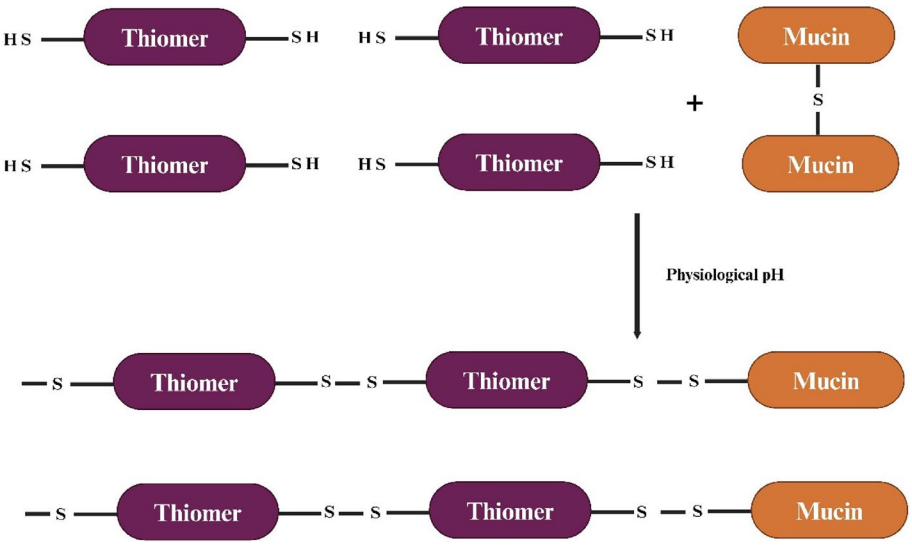

Fig. 6 Thiomer exhibiting inter and intra disulfide bond formation groups delivery

Table 4 Comparison of non-thiolated and thiolated system

(Non-Thiolated) Mucoadhesive Polymer	Thiomer
Attachment by non-covalent connections to mucosal tissues	Strong covalent disulphide linkages bind the thiomer to the mucosa
Display remarkably strong mucoadhesion	Show a remarkable increase in cohesion and adhesion (caused by intra and inter crosslinking)
Several variables, including pH, temperature, and ions, can cause in situ gelation	The pH of the surrounding environment typically initiates the sol–gel transition

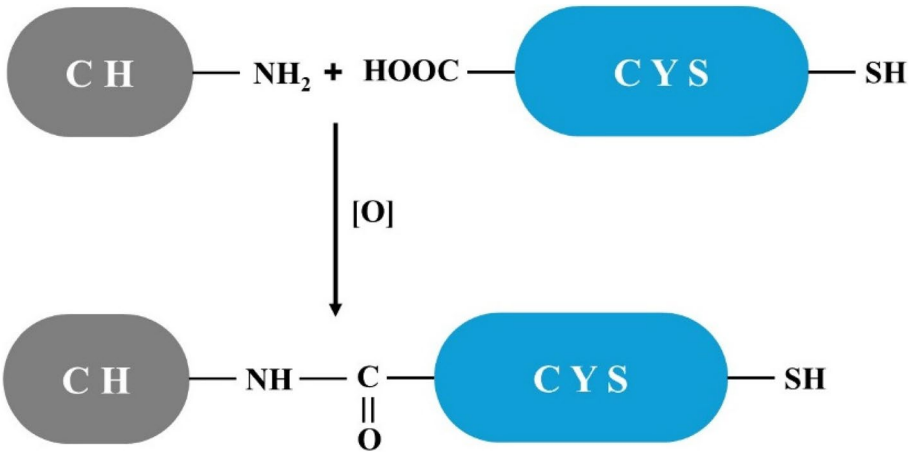

Fig. 7 Thiomerization of Chitosan (CH) with cysteine (CYS)

three sulfhydryl ligands that are often used for anionic thiomers [64]. When compared to the unaltered form, the thiomerization of alginate with the sulfhydryl compound cysteine exhibits superior cohesion, adhesion, stability, and controlled release capabilities. Carbodiimide is added to alginate to activate its carboxylic acid moieties, after which it interacted with the amino group of L-cysteine in an acidic environment. As a result, the primary amino group of the thiol moiety and the carboxylic group of the polymer form an amide link, or covalent

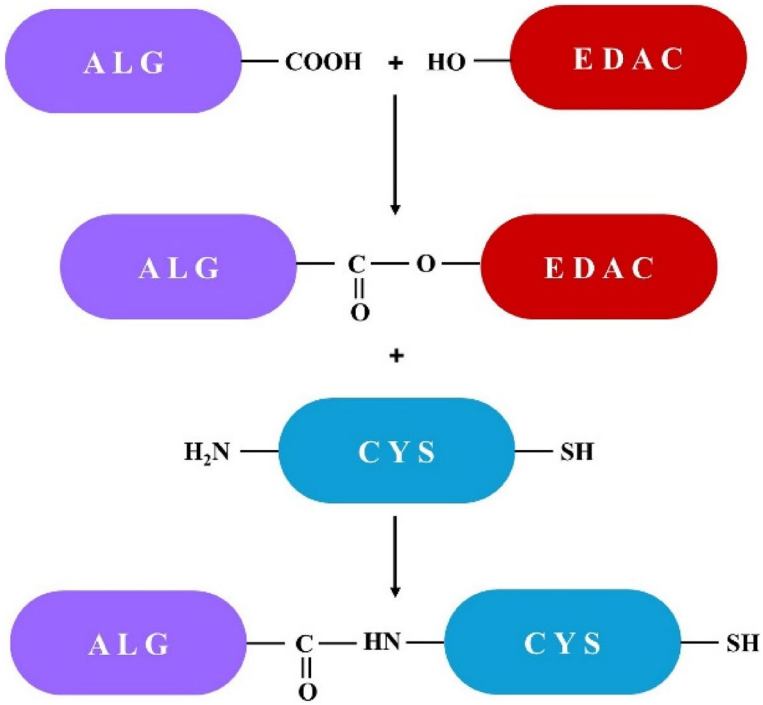

Fig. 8 Thiomerization of alginate (ALG) with EDAC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)

coupling [65]. Although hyaluronic acid (HA), a naturally occurring macromolecular polysaccharide, is being used as a possible drug delivery vehicle, its effectiveness in formulations with extended release is diminished by its quick enzymatic breakdown. Chemically modified HA has gained widespread acceptance as a viable solution to effectively address this issue by cross-linking it with L-cysteine's ethyl ester. Thus, due to the formation of in situ disulphide bonds, this novel system demonstrated a notable improvement in mucoadhesion with sustained release properties. The capacity to generate inter- and/or intra-molecular disulphide bonds enhance a number of desirable properties of the polymer, was demonstrated by a number of delivery systems based on cysteine conjugates of different anionic polymers, such as poly(acrylic) acid, polycarbophil, and CMC [66].

Non-ionic thiomer

Thiomers often exhibit a charged groups on their backbone that are either cationic or anionic. Their flexibility is limited by their ionic nature, despite their impressive functional qualities. Ionic thiomers are frequently linked to drawbacks that restrict their wide range of applications, such as poor cross-linking, pH-dependent drug release, and incompatibility with oppositely charged pharmaceuticals [67] (Table 5). Thiomers based on non-ionizable polymers, such as polyethylene glycol and hydroxyl ethyl cellulose (HEC), have been notion to be the natural option since they provide a wide range of viscosity grades along with desired characteristics including chemical stability, biodegradability, and biocompatibility Fig. 9. By first opening the polymer's rings and then tethering cysteamine, a novel thiolated polymer based on HEC can be produced. Thus, the unmodified polysaccharide originally transformed into an aldehyde form as a result of proximal hydroxyl group oxidation, causing the ring to expand. By reductive amination, the non-ionic polymer changed into a cationic form that readily conjugates with the cysteamine amine ligand. The disadvantages of chitosan thiomers, such as reduced solubility at higher pH ranges (pH > 6), may be lessened by this intriguing conjugate with a positive charge [68].

Pre-activated thiomer

Pre-activated thiomer, a new thiomeric system that improves thiomer stability against unintentional oxidation, was recently reported. This method produces products with remarkably high stability by immobilising well-known polymers on thiomers via disulphide linkage Fig. 10. Thiomers are sometimes also known as "S-protected thiomers" since they stabilised on addition of certain groups via disulphide bonds [86]. By oxidatively combining PAA-cys with 2-mercaptonicotinic acid (2MNA), the preactivated thiomer known as poly(acrylic acid)-cysteine-2-mercaptonicotinic acid (PAAcys-2MNA) has been reported. Compared to the unaltered and thiolated polymers, the

Table 5 Polymeric drug delivery after conjugation with thiol moieties

Charge	Polymer	Thiol moiety	Drug loaded	Route	Ref
Cationic	Chitosan/Glycol chitosan	3Mercapto-propionamide	Dexamethasone	Ocular	[69]
		Mercaptopropionic acid	Ciprofloxacin	Dermal	[70]
		TBA	Acyclovir	Oral	[71]
		N-acetyl cysteine	Tobramycin	Oral	[72]
		TGA	Clotrimazole	Vaginal	[73]
		TGA	Calcitonin	Pulmonary	[74]
Anionic	Poly (acrylic acid)/Carboxy methyl cellulose/Polycarbophil	Cysteine	Diclofenac Sodium	Ocular	[75]
		Cysteine	Econazole & Miconazole	Vaginal	[76]
		Cysteine	Bromelain	Oral	[77]
		Cysteine	vit B_{12}	Oral	[78]
		Cysteine	Paclitaxel	Oral	[79]
		Cysteine and cysteamine	Nystatin	Vaginal	[80]
		Cysteine	Bacitracin	Oral	[81]
		Cysteine	Leu-enkephalin	Nasal	[82]
		Cysteine	Heparin	Oral	[83]
Non-ionic	PEG	Cysteine Mercapto-succinic acid	Cyclosporine A	Ocular	[84]
			Pilocarpine	Ocular	[85]

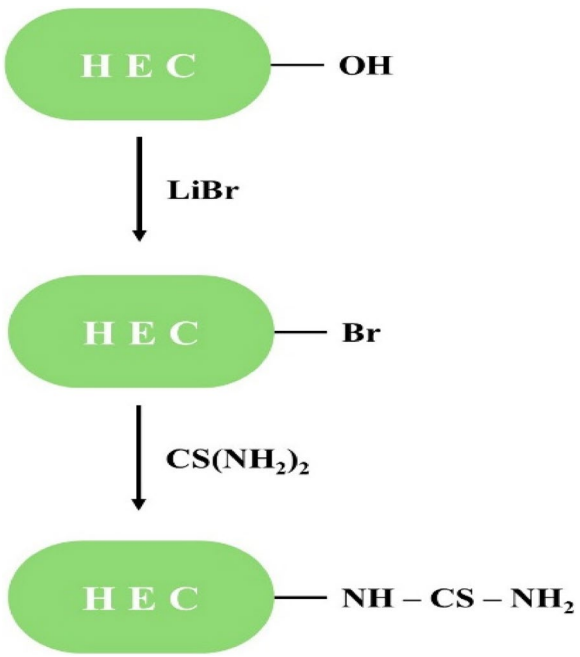

Fig. 9 Thiomerization of HEC with thiourea ($CS(NH_2)_2$) carbodiimide)

resulting conjugates showed much greater swelling and mucoadhesion. Furthermore, the cytotoxicity experiment verified that these pre-activated polymers demonstrated significantly acceptable cell viability [87].

Similarly, 6-(2-acryloylamino-ethyldisulfanyl)-nicotinic acid was copolymerised with acrylic acid to enable the derivation of another new thiomer. The sodium fluorescein level and permeation enhancement ratio were both better with the synthesised pre-activated thiomer. These modified polymers did not exhibit any discernible toxicity in the Resazurin cell-viability test [88].

Functions of thiomers

Mucoadhesive properties

Thiomers have the advantage of developing the covalent bonds between cysteine-rich subdomains of the mucus gel layer and their sulfhydryl residues by forming a disulphide bridges, which are based on thiol/disulfide exchange reactions and/or straightforward oxidation processes, because these forces are known to be weak [64]. The mucoadhesive capabilities of polymers containing sulfhydryl-bearing ligands can be up to 140 times greater than those of unmodified polymers due to presence of these strong covalent interactions [89]. In another study mucoadhesive thiomeric chitosan NPs showed a twofold increase in mucoadhesion, compared to non-thiolated vancomycin. Moreover, in vivo anti-inflammatory results and histopathology demonstrated enhanced healing, suggesting thiomeric chitosan NPs as a promising drug delivering carrier system for ocular delivery of medicament [90].

Cohesive properties

In situ gelling characteristics are demonstrated by both cationic and anionic thiomers by self-crosslinking at physiological pH [91]. When the thiomers come into contact with physiological fluids, the formation of intra- and intermolecular disulphide bonds at the cost of unreacted thiol groups greatly improves the gels' viscoelastic characteristics [66].

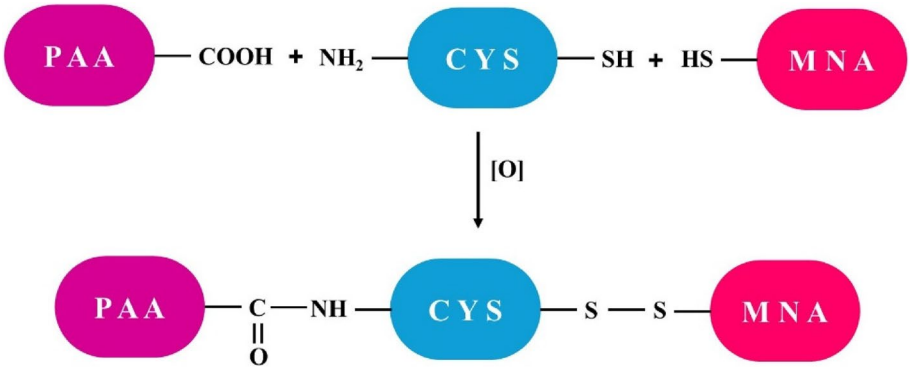

Fig. 10 Synthesis of preactivated thiomer

Protective properties

The enzymatic barrier is one of the most difficult obstacles to peptide medication delivery. Divalent metal ions are necessary for the action of membrane-bound enzymes like aminopeptidase N and luminal-secreted enzymes like the pancreatic proteases A and B. By chelating the polycations, polymers have inhibitory effects on these enzymes. This inhibitory action can be further enhanced against pancreatic peptidases [92] and aminopeptidase N [93] by attaching cysteine to polycarbophil. Szilagyi et. al., developed thiolated poly(aspartic acid) derivatives through oxidant-free disulfide formation for ophthalmic drug delivery. The prepared thiolated composition and mucin showed excellent chemical interaction, suggesting mucoadhesive properties. The biological safety of the polymers was confirmed on kidney cells, showed protective effect and regulated release suggested efficacy higher than conventional dosage form. These results ultimately suggested that developed biopolymers for ophthalmic drug delivery with safety and efficacy [94].

Permeation enhancement

The paracellular absorption of many hydrophilic medications is restricted in non-invasive drug administration by the absorption barrier, which is represented by the membranes of epithelial cells joined by tight junctions. The immobilisation of thiol groups can greatly improve the permeation-enhancing capabilities of polymers. When compared to unmodified polycarbophil without corneal injury, polycarbophil-cysteine demonstrated 2.4 times better dexamethasone phosphate penetration in vitro in ocular drug administration [95]. Thiolated β-cyclodextrin has the potential to enhance mucoadhesive and permeation enhancing properties on ocular mucosa. The results suggested that synthesized modified biopolymers were biocompatible against blood cells through haemolytic assay with no corneal irritation within the tested duration. Moreover, thiolated β-cyclodextrin exhibited 5.3 fold improved aqueous solubility, compared to unchanged β-cyclodextrin. Additionally, thiolated β-cyclodextrin enhanced the permeation of drug by 9.6-, 7.1-, and 5.3- fold on conkunctiva, sclera, and cornea, respectively, suggesting the thiolated β-cyclodextrin might be a promising auxiliary agent for ocular drug delivery [96].

Uptake enhancement

It has been demonstrated that polymers, such as polyethylenglycol and derivatives [97], or pluronic block copolymers [98] can suppress P-gp activity without causing any adverse effects. Using rhodamine-123 as a representative P-gp substrate, the thiomer chitosan-TBA's P-gp-inhibiting action was recently shown during in vitro study. While verapamil 100 μM, which is known to function as a P-gp inhibitor, enhanced the absorptive transport by only 71% [99]. Chitosan-TBA 0.5% (w/v) in conjunction with GSH 0.5% (w/v) resulted in a threefold increase in the absorptive absorption of rhodamine-123. Using the same substrate and thiomer in the form of solid oral drug-delivery devices, Foger and associates could validate these results in vivo in rats [100].

Controlled drug release

Delivery methods with sustained release are necessary for many medications, particularly those with potent pharmacological effects, to maintain a steady plasma level and prevent adverse effects brought on by peaks or depths in the plasma level. The stability of thiomer matrices is significantly enhanced on formation of disulphide bond within the thiolated polymers, ensuring a drug release over several hours. Diffusion, which results from the swelling characteristics of the thiomer matrix, ionic interactions in between thiomer and drug, and the drug's solubility coefficient in general are trigger mechanisms for release [101].

Formulation of thiomer or modified thiomers-based nano-medicine in management of ocular infections

Drug delivery based on ocular nanotechnology is a specialized technique that uses nanoscale carriers or systems to precisely deliver therapeutic drugs to the eye. These carriers improve stability and solubility, extend release, lessen side effects, and deliver drugs to the intended location. Over the past 20 years, this method has drawn interest for its capacity to improve drug bioavailability and overcome ocular obstacles. Nanoparticles (NPs), both organic and inorganic, provide an innovative approach to achieve therapeutic needs, notably in the ocular disciplines, with a notable enhancement in drug delivery. As a result, Numerous compositions of nanoparticles have been developed, including lipid-based nanoparticles, nanosuspension, nanoemulsion, and metal-based nanoparticles [102].

Polymeric nanoparticles

NPs are tiny particles that range in size from 1 to 1000 nm. They can be composed of a number of different materials, such as metals (like gold or silver [103–114]), polymers [10], lipids [9, 12, 115–117], ceramics [118], and other substances. Nanocarriers like nanoparticles offer a wide range of uses in ophthalmology because they can transport ocular drugs to precise target areas. The production of NPs involves the use of various biodegradable polymers, including poly (lactic acid). A variety of natural polymers, including albumin, chitosan, gelatin, sodium alginate, and poly (epsilon-caprolactone), poly (alkyl cyanoacrylate), and poly (lactic-co-glycolic acid), can help deliver medications to the tissues of the eyes. Chitosan-based NPs degrade fast until combined with multivalent anionic substances like sodium sulphate or alginate, which triggers an ionic cross-linking mechanism that stabilizes the system [119]. However, since disulphide bonds develop inside the polymeric network, thiolated chitosan-based NPs do not disintegrate, resulting in controlled drug release and robust microparticle stabilization. When multivalent anionic chemicals are added to thiolated chitosan-based NPs, the mucoadhesion properties are greatly increased over chitosan due to the immobilization of thiol groups on chitosan [120].

A modified form of thiolated chitosan, thiolated chitosan-sodium alginate NPs (TCS-SA NPs) showed good in vitro cytocompatibility and increased drug delivery into HCE cells in vitro and cornea in vivo, suggesting good potential for ocular drug delivery [113]. TCS-SA NPs had a high degree of thiol substitution of TCS up to 1,411.01 ± 4.02 μmol/g. The thiolated chitosan-based nanoparticulate prulifloxacin in situ gel, which had a mean particle size of 16 nm and an 80% drug entrapment efficiency, demonstrated a pH of about 7.2 ± 0.2, good mucoadhesion qualities, non-irritability, and prolonged drug release across the cornea.

Hydrogel

Three-dimensional hydrophilic polymeric networks, or hydrogels, can be made with a variety of natural and synthetic hydrophilic polymers, such as hyaluronic acid, polyvinyl alcohol, and chitosan [121]. Hydrogel are mainly used in Ocular drug delivery because its viscous nature offers a relatively extended retention of trapped medications at the application location while their transparency reduces blurring of vision [122]. At the beginning of the 2000s, researchers created a thiolated hyaluronic-based hydrogel using air and hydrogen peroxide oxidation [123]. Disulphide bridges can be formed between hyaluronic acid chains by oxidation or thiol-disulfide exchange events. Numerous research groups have thoroughly examined the strategies for producing in situ gelling hydrogels without the addition of any adjuvant or cross-linking agent [124]. Thiol-ene reactions have also been used to develop a variety of biocompatible cross-linked hydrogels based on HA, either by radical-initiated reactions or nucleophilic processes, including Michael addition reactions with vinyl sulfone or acrylates [125].

Shorter gelation times are optimal for preventing medicine loss from the ocular surface [126]. A thiolated carboxymethyl hyaluronic acid-based veterinary eye drop formulation was created to enhance medication and cell transfer, offer local lubrication, and treat corneal ulcers. In tests on dogs and cats, these hydrogels showed that wounds healed in 7–13 days. Combining HA hydrogel with growth factors can encourage the migration and proliferation of cells, which will enhance the repair of eye injuries. Moreover, antibiotics can be delivered via HA-based hydrogel [127]. Thiolated cyclodextrins also participate in photo-initiated thiolene reactions with diallyl-PEG. Because of the hydrogel's poor hydrophilicity and high cyclodextrin ratio, the hydrogels with the shortest PEG chain length were able to contain the most puerarin, a glaucoma drug. Despite an early burst release, the medication was released consistently [128].

Dendrimers

Dendrimers are three-dimensional, globular, branched, tree-like macromolecules with a central core where a drug can be conjugated, encapsulated, or trapped, have been applied for the entrapment and subsequent delivery of oligonucleotides, hydrophilic and hydrophobic drugs. Both anionic (polycarbophil, carboxymethylcellulose, alginates) and cationic (chitosan, polyasprtamide) polymers have been used to synthesise and analyse a variety

of thiomers, with varying degrees of success [129]. However, the thiomers now available have a limited thiol content (up to one mole of thiol per mole of polymer), which may mean that a high polymer content in the unit dosage form is required to obtain acceptable covalent type adhesion [170]. Cysteine, a thiol-introducing ligand, and anionic dendrimers (G3.5 PAMAM) are used to create the thiolated dendrimers. The impact of the cysteamine molar ratio on the conjugate's synthesis, infrared analysis, and intrinsic properties like thiol and disulphide content, as well as the influence of pH on these properties, are all thoroughly assessed and examined. Recent clinical product, Puerarin eyedrops (1%, w/v) demonstrated a brief residence period, low ocular absorption, and low bioavailability. When used in puerarin formulations, PAMAM dendrimers (0.2%) demonstrated acceptable toxicity and enhanced permeability on excised cornea [130]. PAMAM dendrimers were used to administer dexamethasone to the cornea using iontophoresis. Complexed with G3.5 and G4 dendrimers, dexamethasone had better solubility, allowing better corneal transport and longer aqueous humour retention. PAMAM dendrimers' enhanced penetration effect was also responsible for this efficiency boost, demonstrating its suitability as a topical medication delivery tool for the eye [131].

Liposome

Liposomes are bilayered lipid vesicles made of cholesterol and phospholipids that can entrap either or both hydrophilic and hydrophobic medicines. They have a central water compartment width of 0.025 to 10 µm. Thiomers have demonstrated several encouraging characteristics for drug administration, such as improved permeability, inhibition of the efflux pump, inhibition of enzymes, and mucoadhesion [132]. Liposomes coated with "S-protected thiomers" to improve their penetration and efflux pump inhibitory properties that are durable against oxidation [133]. The feasibility of developing liposomes coated with the multifunctional polymer PAA-Cys (poly (acrylic acid)-cysteine) was investigated. Both cationic submicron liposomes and cationic multilamellar vesicles were developed and coated with PAA-Cys. These carriers' dimensions, zeta potential, quantity of free thiol groups, aggregation behaviour, drug loading, and drug release were all investigated. The results demonstrated that producing PAA-Cys-coated liposomes is feasible and that they satisfy the essential requirements for stability, drug loading, and dispersion for an intended use in oral drug administration [134]. A study reported that the PC-based liposomal system was integrated into a deacetylated gellan gum-based gel formulation to deliver timolol maleate in a hybrid formulation. According to ex vivo permeation measurements conducted on isolated rabbit corneas, the liposomal system's apparent permeability coefficient increased by 1.93 times. Additionally, the hybrid system doubled the length of the therapeutic impact in rabbits compared to solution-based formulations, and it demonstrated superior efficacy and improved the retention time of liposomes on the corneal surface by up to 10 min. These findings show that liposome-based hybrid DDS is successful in the treatment of anterior eye disorders.

Nanosuspension

Nanosuspensions (NSs) are made up of stabilisers and pure drug nanoparticles with an average diameter of less than 1 µm (usually between 200 and 500 nm). They can be made in liquid phases that are either aqueous or non-aqueous, improving the solubility of drugs in both organic and salty environments [135]. NSs are a flexible way to enhance the administration of hydrophobic medications and have the potential to improve the effectiveness of medicines that are not highly water soluble, especially those derived from natural sources. A variety of production techniques are employed, including top-down techniques like co-grinding, high-pressure homogenisation, wet milling, and dry milling, as well as bottom-up techniques like anti-solvent precipitation, liquid emulsion, and sono-precipitation. NSs in ocular DDSs allow for the delivery of higher amounts of poorly soluble drugs while also increasing residence time in the cul-de-sac [136]. Research showed that diclofenac-loaded cationic nanosuspension made of chitosan and methoxy poly (ethylene glycol)-poly (ε-cap rolactone) di-block co polymer was effective in treating ocular irritation. In an albino rabbit model, the polymeric nanosuspension demonstrated twice the area under the curve and a greater C_{max} in aqueous humour, indicating improved bioavailability. The chitosan-coated NSs demonstrated improved corneal penetration and retention in the in vivo corneal penetration test with no irritation in the eyes. Furthermore, after 24 h, the NSs remained extremely stable in an aqueous humour solution [137]. Amikacin's ocular bioavailability was increased using a polymeric NSs combining Eudragit® RL 100 and Eudragit® RS 100 to effectively treat anterior eye *Staphylococcus aureus* infections. In addition, a combination moxifloxacin and pamoic acid nano solution developed using an ion pairing process with mucus penetrating characteristics was investigated for the treatment of bacterial keratitis. The results of the pharmacokinetic study showed that the drug was dispersed uniformly throughout the tissues of the anterior eye, including the aqueous humour [138]. Moreover, to treat fungal keratitis, a quasi-emulsion solvent evaporation technique was employed to produce Eudragit® RS 100, a voriconazole-based NSs. N-methyl-2-pyrrolidone (Pharmasolve®) was added to the formulation to increase

ocular permeability. The solution greatly reduced the development of *Candida albican* and shown good ocular permeability [139].

Microemulsions and nanoemulsions

Microemulsions are colloidal dispersions of water/oil or oil/water that are thermodynamically stable and stabilised by a surfactant [140]. Although the formulation components of micro and nanoemulsions are identical, their stability is different. Nanoemulsion is thermodynamically unstable, whereas microemulsion is thermodynamically stable [141]. The use of microemulsions and nanoemulsions for ocular medication administration is becoming more popular due to associated advantages with their high surface area and small droplet size. High drug solubility, non-irritating properties, enhanced corneal permeability, enhanced bioavailability, extended shelf life, ease of formulation, and the capacity to give both hydrophilic and hydrophobic medications are some of these advantages [142]. Research showed that a mucoadhesive nanoemulsion of cyclosporine A was developed and modified utilising the pseudo-ternary phase diagram in order to improve the retention and bioavailability of cyclosporine A in treating ASED, such as corneal allograft rejection and DED. Gamma scintigraphy study revealed that the nanoemulsion was gradually eliminated from the ocular surface. Additionally, the drug's concentrations in the cornea and conjunctiva were within therapeutic levels for the whole day. The chitosan-coated nanoemulsion of cyclosporine A shows potential in treating immunologically associated anterior eye diseases due to its improved biodistribution and sustained contact with the ocular surface [143].

Native/modified thiomers-based drug delivery system in management of ocular complication

Thiomers, which are modified polymers containing thiol groups, have emerged as promising materials for ocular drug delivery systems. These thiolated polymers can form covalent disulfide bonds with mucin on the ocular surface, enhancing mucoadhesion and prolonging the retention of drug formulations. This property is particularly beneficial for managing ocular complications such as dry eyes syndrome, where thiomers can stabilize the tear film and improve drug bioavailability. Thiomers can be used in fabrication of various delivery systems, including eye drops and ocular inserts that has shown good tolerance and stability in clinical studies. Thus, by improving drug retention and release profiles, thimers offer a potential solution to overcome the challenges associated with traditional ocular drug delivery methods, such as short drug retention times and low bioavailability. The application of native/modified thiomers-based formulations in management of various ocular complications have been elaborated below.

Cataract

A cataract is a region of the eye's lens that becomes clouded and reduces vision. Nanomedicine formulations have been investigated to improve the bioavailability, biocompatibility, and biodegradability of anti-cataract medications. When curcumin was encapsulated in PLGA nanoparticles for systemic delivery, the oral bioavailability of the medication was nine times higher than that of free curcumin. Lutein can be loaded into a nanoemulsion using Labrasol®, a non-ionic surfactant excipient. This type of nanoemulsion has a shorter lag time and twice as much cellular accumulation as free lutein. It has also been found that liposomes are an effective formulation for cataract prevention. For example, vitamin E-containing liposomes made of dipalmitoyl phosphatidylcholine and dioleoyl phosphatidylcholine were found to reduce the development of cataracts in a rat model. Moreover, cytochrome C-loaded freeze-dried liposomes shown notable effectiveness in delaying the development and advancement of cataracts in rats [144].

Glaucoma

Damage to the optic nerve is a common feature of glaucoma, a group of eye disorders. Among the active ingredients used to treat glaucoma include rho-kinase inhibitors, β-blockers, α-agonists, prostaglandin analogues, and carbonic anhydrase inhibitors. Comparing pilocarpine-containing poly (butyl cyanoacrylate) nanospheres to conventional pilocarpine solutions was the first investigation into the use of nanomedicine formulations to treat glaucoma. Liao et al. developed pilocarpine-loaded gelatin-covered mesoporous silica nanoparticles (p/GM) in order to achieve a sustained drug release. By adjusting its thickness on the mesoporous silica NPs, the gelatin coating was managed. The results showed that pilocarpine may be released in a high-concentration (~ 50%) and long-lasting (up to 36 days) form at p/GM0.05, or 0.05 mg of gelatin coating per mg of NPs, enabling the maintenance of normal intraocular pressure for up to 21 days [145]. Glaucoma, a group of eye disorders, often causes damage to the optic nerve. Antiglaucoma medications like β-blockers and carbonic anhydrase inhibitors are encapsulated in chitosan nanoparticles, which have shown effectiveness in lowering intraocular pressure. Additionally, a formulation of latanoprost in long-lasting unilamellar liposomes has been fabricated. A formulation of long-lasting unilamellar liposomes for the delivery of the prostaglandin derivative latanoprost (Xalatan®) was reported by Natarajan et al. A single subconjunctival injection of liposomes containing latanoprost was found

to lower intraocular pressure for up to 120 days. A second injection was given, and over another 180 days, the IOP decreased even more [146].

Age-related macular degeneration

AMD is a complicated ocular condition marked with a loss of progressive central vision brought on by neovascular and degenerative changes in the macular region, which gives the posterior part of the eye its central and crisp vision. The most common treatment for AMD is anti-vascular endothelial growth factor (anti-VEGF) medications, while additional treatments include photodynamic therapy, transpupillary thermotherapy, radiation, and retinal translocation [147]. Currently, Eylea® (aflibercept), Lucentis® (ranibizumab), and Avastin® (bevacizumab) are the three most often used anti-VEGF drugs. Ranibizumab is a small portion of an antibody against VEGF-A, whereas bevacizumab is a full anti-VEGF-A immunoglobulin. The two primary components of the distinct recombinant fusion protein Aflibercept are the extracellular domains of human vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGFR-2, which make up VEGF-binding areas. By binding to placental growth factor, VEGF-A, or VEGF-B, aflibercept can decrease angiogenesis. Intravitreally delivering anti-VEGF medications to the retina reduces dosage requirements and circumvents systemic administration's negative effects. Several liposome formulations, including PEGylated cationic liposomes, vector–mediated liposomes, and peptide-modified PEGylated liposomes, are presently being investigated for the treatment of AMD [148]. Tavakoli et al. synthesized sunitinib-loaded liposomes which inhibit the tyrosine kinase of vascular endothelial growth factor receptors, hence blocking the neovascularisation signalling cascade. They demonstrated that sunitinib could be efficiently transported by liposomes with a mean size of 104 nm and released for up to three days [149].

Diabetic retinopathy

An eye consequence of diabetes is known as DR. It is characterized as microvascular condition that damages blood vessels and light-sensitive retinal structures, causing capillary blockage. Corticosteroids, AGE inhibitors like carnosine, and antioxidants are common medications used to treat diabetic retinopathy. It has been investigated to administer these medications to treat DR using polymeric nanospheres. High drug encapsulation rates in polyvinyl alcohol, poly (methyl methacrylate), chitosan, and PLGA nanospheres prolong the duration of free drug residence. DR is commonly treated with liposome formulations mostly based on biodegradable lipids, such as phospholipids, ceramides, and glycerides. Entrapping drugs in a dendrimer network made up of functional groups can facilitate long-term drug delivery to the retina [150].

Atopic dermatitis

When evaluating keratoconus or glaucoma, ophthalmologists performing corneal refractive surgery must consider the control group (523.45 ± 18.3 μm). Researcher looked at the impact of AKC onset on the ocular surface in a study. The result demonstrated that the more severe the AKC-induced damage to the ocular surface epithelium, the earlier it starts and the longer it persists. For AKC patients whose illness began in childhood, conjunctival squamous metaplasia, goblet cell loss, tear film instability, and epithelial degradation were markers of worse prognosis [151].

Toxicological reports on thiomer-based nanomedicine in the management of ocular complications

The study evaluated the cytotoxicity and biocompatibility of unmodified sodium alginate and newly produced from scratch sodium alginate (SA-cys) using L-929 murine fibroblast cells. The cells treated with active components showed that SA-cys and unmodified sodium alginate exhibited comparable levels of biocompatibility and cytotoxicity [65]. In another study, RPE cell cultures exposed to NXM3 blank and NXM3 MXF-loaded NPs suggested that the number of MXF-loaded NPs in the culture media did not substantially impact the cell survival. Following 24 h of incubation, > 80% of cells were still alive, with no distinct changes in cell shape under a microscope. The findings indicated that the prepared product were not toxic to RPE cell cultures, a crucial requirement for biomedical applications [152].

Preclinical and clinical aspects

The in vivo trans corneal behaviour of medicines in rabbit eyes was observed using an inverted fluorescence microscope. The rabbit eyeballs were sectioned vertically along the sagittal plane after euthanasia. The findings demonstrated that ocular medication penetration was considerably enhanced by surface-modified nanostructured lipid carriers (NLCs) coated with chitosan-N-acetylcysteine (CS-NAC). Compared to chitosan-coated NLCs (CH-NLCs), CS-NAC NLCs showed greater fluorescence intensity and deeper penetration across the cornea, exhibiting the greatest green fluorescence, which shows that there is the medication, in the corneal epithelium. These results suggested that NLCs treated with CS-NAC enable more efficient drug delivery across the ocular barrier [153]. In comparison to the unmodified polycarbophil, penetration

of dexamethasone phosphate and sodium fluorescein increased by 2.2 and 2.4 times, respectively, in the rabbit cornea treated using polycarbophil–cysteine, according to in vitro research. Rabbit corneas showed no signs of toxicity. Because of the thiomers' in situ gelling and mucoadhesive qualities, the formulation remains in place for a longer amount of time, which leads to a longer duration of drug absorption. The integrated medicines' bioavailability will be further enhanced by their permeation-enhancing qualities [154].

Clinical investigations on this unique class of polymers have been conducted in large numbers, demonstrating the use of thiomers. Researchers have advanced from employing numerous animal models in vitro and in vivo investigations to examine on humans. Hornof and his associates set out to develop a thiolated poly (acrylic acid) ocular insert that could regulate the administration of eye medications. They also aimed to evaluate this insert's efficacy in vivo. The study assessed the inserts' in vitro medication release, water absorption, and swelling behaviour. In vivo experiments using fluorescein were used to investigate the substance's tolerability and release properties in human subjects. According to the study, thiolated polyacrylic inserts showed a regulated release of fluorescein and sustained a high concentration on the surface of the eye for more than eight hours. This implies that the altered inserts might be a good choice for delivering drugs into the eyes [155]. In two cohorts of 18 healthy participants, a clinical trial evaluated the safety and tolerability of eye drops containing chitosan-N-acetylcysteine at different doses for treating dry eye syndrome. With just two incidences of conjunctival redness and one case of moderate epithelial keratitis, the eye drops showed a good safety profile [156]. To determine how well Lacrimera (chitosan-N-acetylcysteine) eye drops treat moderate-to-severe dry eye illness is a real-world clinical situation, Nepp and his colleague carried out a clinical trial. The main goal was to evaluate treatment's progress results. Twenty-five subjects who received treatment using Lacrimera were the subject of a retrospective analysis in this study. After a month of treatment, the results showed a discernible improvement in Schirmer's score and tear breakup time. The proportion of patients who had intact corneas increased significantly, from 12 to 64%. 29% of patients said Lacrimera was helpful in reducing their symptoms, the study found. For at least a month, the drops were judged to be both safe and successful in treating dry eye condition [211]. Research by Durie et al. investigated the safety and efficacy of a crosslinked thiolated carboxymethyl hyaluronic acid liquid-gel ocular bandage for promoting reepithelialisation in corneal defects following photorefractive keratectomy. The results showed that the gel significantly reduced the reepithelialisation period and was well tolerated by the patients [157].

Challenges in fabrication of native/modified thiomer-based nanomedicine for its ocular applications

Drug absorption is constrained by the protective layers in eyes, including the retinal barrier, corneal epithelium, or tear film. One of the biggest challenges is creating thiomer-based carriers that can successfully get through these barriers without endangering ocular safety. In order to improve permeability while preserving compatibility with ocular tissues, sophisticated engineering techniques are needed [158]. Because thiomers are known to be mucoadhesive, they stay on mucous membranes including the surface of the eye—for longer. Finding the perfect balance between adhesion and avoiding toxicity or pain can be challenging, despite the fact that this trait is beneficial for prolonged drug administration. Although pre-activated thiomers with improved adhesion qualities show promise, controlling their interactions with the tear film and mucous layer remains difficult. According to the report, more investigation is required to improve these interactions for improved treatment outcomes. Thiomers face significant challenges with cost-effectiveness and scalability, despite their potential for a variety of biomedical applications. Many thiomer-based formulations can be challenging to create on a big scale because they require sophisticated stabilizing and synthesizing methods. Additionally, the fabrication method must maintain the stability and efficacy of these compositions while controlling manufacturing costs. The complexity of the synthesis and the need for precise quality control make it challenging to scale up thiomer manufacture, which may limit their widespread clinical use [159].

Regulatory aspects and Patents

The USFDA, the European Medicines Agency, and national medical agencies in Europe are among the responsible agencies that address patient safety, efficacy, and quality resulting from the use of nanomedicines [160]. The potential effects on the environment during manufacturing, after use, and after disposal. The FDA is having difficulty developing a criterion to guarantee the safe and effective development of nanoproducts, whether they be drugs, devices, or biologics, because they lack the data necessary to assess the safety to humans and the environment. In response to complaints regarding their lack of regulation of nanoparticles, the FDA published a first draft guidance in June 2011. However, a definitive guidance document for nanoparticles in medicine has not yet been created.

Various addition and omission criteria are there based on habitat-related consequences for the evaluation of medicinal items in the USA and the EU. All applications for marketing authorization in the EU must go through a pre-screening phase that includes a preliminary estimate of the anticipated ecological concentration of water present on the surface, with a permissible confine of 0.01 ppb, and an environmental risk assessment [161]. Therefore, no more steps are taken for the product's environmental risk assessment is considered valid if the estimated environmental concentration is below this and no other environmental concerns are present. Unless they are exempt, the FDA in the USA uses an environmental evaluation for new medication applications; however, an exemption cannot be granted in case the predicted concentration in the environment is greater than 1 ppb.

A US patent (US20230056811A1) outlines a mucoadhesive system that uses preactivated thiomers to improve drug retention in the eye. This invention offers mucoadhesive solid or semisolid ocular delivery systems and is related to the field of ophthalmic formulations. Based on a matrix of preactivated thiomers, the invention's delivery techniques are best suited as ocular films or inserts. The invention's delivery systems help to deliver drug to the eyes to address conditions including glaucoma and dry eye, among others. The invention's distribution methods can also be applied to treat eye disorders [162].

Conclusion

Thiomer-based nanomedicines have much potential for ocular medication delivery because they can solve many problems with traditional therapies. They are perfect candidates for treating various ocular disorders due to their unique characteristics, which include superior mucoadhesion, biocompatibility, and the capacity to increase medication absorption. The advancements in the use of thiomer and modified thiomer-based systems in the treatment of ocular issues, including diabetic retinopathy, cataracts age-related macular degeneration, & other eye-related diseases, are highlighted in this study. The findings of thiomer-based nanomedicine research have shown promising results in enhancing the results of treatment and providing a more efficient and patient-friendly substitute for conventional techniques. Notwithstanding the encouraging outcomes, more investigation is required to address current issues with their manufacturing and regulatory approval procedures. Thiomer-based ocular drug delivery systems have a promising future ahead with ongoing advancements that should improve their effectiveness, safety, and clinical application, which will eventually improve patient care and quality of life.

Acknowledgements
This work was partially supported for Sudarshan Singh by CMU Proactive Researcher Scheme (2023), Chiang Mai University for Sudarshan Singh. Dr. Biswajit Basu, extends his sincere appreciation to the Adamas University, India, for their generous support that enabled the completion of this work.

Authors' contributions
Biswajit Basu and Sudarshan Singh: conceptualization, writing, reviewing, and editing. Suraj Mallick, Suman Dhauria, and Anisha Das: data collection, writing original draft.

Funding
This work has not received funds from any profitable or non-profitable organization.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Received: 2 January 2025 Accepted: 8 March 2025
Published online: 02 April 2025

References

1. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol. 2012;96(5):614–8.
2. Schoenfeld ER, et al. Patterns of adherence to diabetes vision care guidelines: baseline findings from the Diabetic Retinopathy Awareness Program. Ophthalmology. 2001;108(3):563–71.
3. Zhao J, et al. Causes of visual impairment and blindness in the 2006 and 2014 nine-province surveys in rural China. Am J Ophthalmol. 2019;197:80–7.
4. Kumar A, et al. Sustainable and consumer-centric nanotechnology-based materials: An update on the multifaceted applications, risks and tremendous opportunities. Nano-Structures & Nano-Objects. 2024;38: 101148.
5. Patel R, et al. Development and characterization of curcumin loaded transfersome for transdermal delivery. J Pharm Sci Res. 2009;1(4):71.
6. Singh S, et al. Poly (vinyl alcohol)-gelatin-sericin copolymerized film fortified with vesicle-entrapped demethoxycurcumin/bisdemethoxycurcumin for improved stability, antibacterial, anti-inflammatory, and skin tissue regeneration. Int J Biol Macromol. 2024;258: 129071.
7. Singh, S., et al., Polymeric scaffold integrated with nanovesicle-entrapped curcuminoids for enhanced therapeutic efficacy. Nanomedicine, 2024: p. 1–17.
8. Dave, J., et al., Polyol-modified deformable liposomes fortified contact lenses for improved ocular permeability. Nanomedicine, 2025: p. 1–14.
9. Sudarshan, S., et al., Lipid Nanoparticulate Drug Delivery Systems: Approaches toward Improvement in Therapeutic Efficacy of Bioactive Molecules:, in Drug Carriers, V.-G. Luis Jesús, Editor. 2022, IntechOpen: Rijeka. p. Ch. 7.
10. Patel RP, et al. Alginate Nanoparticles: A Potential Drug Carrier in Tuberculosis Treatment. In: Shegokar R, Pathak Y, editors., et al., Tubercular Drug Delivery Systems: Advances in Treatment of Infectious Diseases. Cham: Springer International Publishing; 2023. p. 207–34.
11. Bhattacharya, S., B.G. Prajapati, and S. Singh, Chapter 8 - Polymeric nanoparticles in colorectal cancer, in Colorectal Cancer, B.G. Prajapati, A.K. Philip, and S. Bhattacharya, Editors. 2024, Academic Press. p. 203–231.
12. Das, U., et al., Unveiling the potential of chitosan-coated lipid nanoparticles in drug delivery for management of critical illness: a review. Zeitschrift für Naturforschung C, 2024.

13. Parihar, A., et al., Chapter 7 - Novel targeting formulations in colorectal cancer, in Colorectal Cancer, B.G. Prajapati, A.K. Philip, and S. Bhattacharya, Editors. 2024, Academic Press. p. 175–201.
14. Singh, S. and Y. Murti, Chapter 9 - Nanotherapeutics in ocular infections, in Applications of Nanotherapeutics and Nanotheranostics in Managing Infectious Diseases, A. Kumar and P. Parashar, Editors. 2025, Academic Press. p. 187–204.
15. Flaxman SR, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(12):e1221–34.
16. Liu L-C, Chen Y-H, Lu D-W. Overview of Recent Advances in Nano-Based Ocular Drug Delivery. Int J Mol Sci. 2023;24(20):15352.
17. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive nanoparticulate systems for peptide drug delivery. Adv Drug Deliv Rev. 2001;47(1):39–54.
18. Balenga NAB, et al. Protective efficiency of dendrosomes as novel nano-sized adjuvants for DNA vaccination against birch pollen allergy. J Biotechnol. 2006;124(3):602–14.
19. Langguth P, et al. Nanosuspension formulations for low-soluble drugs: pharmacokinetic evaluation using spironolactone as model compound. Drug Dev Ind Pharm. 2005;31(3):319–29.
20. Cuenca AG, et al. Emerging implications of nanotechnology on cancer diagnostics and therapeutics. Cancer. 2006;107(3):459–66.
21. Alvarez-Rom# x, E., et al., Enhancement of topical delivery from biodegradable nanoparticles. Pharmaceutical research, 2004. 21: p. 1818–1825.
22. Wong HL, et al. A new polymer–lipid hybrid nanoparticle system increases cytotoxicity of doxorubicin against multidrug-resistant human breast cancer cells. Pharm Res. 2006;23:1574–85.
23. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery–a review of the state of the art. Eur J Pharm Biopharm. 2000;50(1):161–77.
24. Ding S. Recent developments in ophthalmic drug delivery. Pharm Sci Technol Today. 1998;1(8):328–35.
25. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009;71(3):505–18.
26. Kels BD, Grzybowski A, Grant-Kels JM. Human ocular anatomy. Clin Dermatol. 2015;33(2):140–6.
27. Mandal A, et al. Polymeric micelles for ocular drug delivery: From structural frameworks to recent preclinical studies. J Control Release. 2017;248:96–116.
28. Dartt DA, Willcox MDP. Complexity of the tear film: Importance in homeostasis and dysfunction during disease. Exp Eye Res. 2013;117:1–3.
29. Gorantla S, et al. Nanocarriers for ocular drug delivery: current status and translational opportunity. RSC Adv. 2020;10(46):27835–55.
30. Subrizi A, et al. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug Discovery Today. 2019;24(8):1446–57.
31. Geroski DH, Edelhauser HF. Transscleral drug delivery for posterior segment disease. Adv Drug Deliv Rev. 2001;52(1):37–48.
32. Coca-Prados M. The blood-aqueous barrier in health and disease. J Glaucoma. 2014;23:S36–8.
33. Peynshaert K, et al. In vitro and ex vivo models to study drug delivery barriers in the posterior segment of the eye. Adv Drug Deliv Rev. 2018;126:44–57.
34. Rahman M, et al. Synthesis and characterization of functionalized Se-MCM-41 a new drug carrier mesopore composite. Orient J Chem. 2017;33(2):611.
35. Paggi CA, et al. Joint-on-chip platforms: entering a new era of in vitro models for arthritis. Nat Rev Rheumatol. 2022;18(4):217–31.
36. Cunha-Vaz, J., R. Bernardes, and C. Lobo, Blood-retinal barrier. European journal of ophthalmology, 2011. 21(6_suppl): p. 3–9.
37. Thrimawithana TR, et al. Drug delivery to the lens for the management of cataracts. Adv Drug Deliv Rev. 2018;126:185–94.
38. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–11.
39. Nadhira AM, Djatikusumo A, Victor AA. Brolucizumab for Neovascular Age-Related Macular Degeneration in Real-World Setting. International Journal of Retina. 2023;6(2):130–130.
40. Gonzalez VH, et al. Early and long-term responses to anti–vascular endothelial growth factor therapy in diabetic macular edema: analysis of protocol I data. Am J Ophthalmol. 2016;172:72–9.
41. Hsu JI, Pflugfelder SC, Kim SJ. Ocular complications of atopic dermatitis. Cutis. 2019;104(3):189–93.
42. Tsai C-H, et al. Ocular drug delivery: Role of degradable polymeric nanocarriers for ophthalmic application. Int J Mol Sci. 2018;19(9):2830.
43. Sen HN, et al. Periocular corticosteroid injections in uveitis: effects and complications. Ophthalmology. 2014;121(11):2275–86.
44. Jager RD, et al. Risks of intravitreous injection: a comprehensive review. Retina. 2004;24(5):676–98.
45. Paliwal H, et al. Novel Approaches in the Drug Development and Delivery Systems for Age-Related Macular Degeneration. Life. 2023;13(2):568.
46. Del Amo EM, et al. Pharmacokinetic aspects of retinal drug delivery. Prog Retin Eye Res. 2017;57:134–85.
47. Hornof M, Toropainen E, Urtti A. Cell culture models of the ocular barriers. Eur J Pharm Biopharm. 2005;60(2):207–25.
48. Sigurdsson HH, et al. Topical and systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye. Acta Ophthalmol Scand. 2007;85(6):598–602.
49. Yellepeddi VK, Palakurthi S. Recent advances in topical ocular drug delivery. J Ocul Pharmacol Ther. 2016;32(2):67–82.
50. Waite D, et al. Posterior drug delivery via periocular route: challenges and opportunities. Ther Deliv. 2017;8(8):685–99.
51. Ranta V-P, et al. Barrier analysis of periocular drug delivery to the posterior segment. J Control Release. 2010;148(1):42–8.
52. Gyarmati B, Krisch E, Szilágyi A. In situ oxidation-induced gelation of poly (aspartic acid) thiomers. React Funct Polym. 2014;84:29–36.
53. Eze FN, Jayeoye TJ, Singh S. Fabrication of intelligent pH-sensing films with antioxidant potential for monitoring shrimp freshness via the fortification of chitosan matrix with broken Riceberry phenolic extract. Food Chem. 2022;366: 130574.
54. Pawar A, et al. Chitosan fortified repaglinide gastro-retentive mucoadhesive microsphere with improved anti-diabetic attribute. Intelligent Pharmacy. 2024;2(3):441–9.
55. Singh S, et al. Chitosan-poly(vinyl alcohol) intelligent films fortified with anthocyanins isolated from Clitoria ternatea and Carissa carandas for monitoring beverage freshness. Int J Biol Macromol. 2021;182:1015–25.
56. Mohite P, et al. Potential of Chitosan/Gelatin-Based Nanofibers in Delivering Drugs for the Management of Varied Complications: A Review. Polymers. 2025;17(4):435.
57. Jin X, et al. Chitosan–glutathione conjugate-coated poly (butyl cyanoacrylate) nanoparticles: promising carriers for oral thymopentin delivery. Carbohyd Polym. 2011;86(1):51–7.
58. Bernkop-Schnürch A, Greimel A. Thiomers: The next generation of mucoadhesive polymers. Am J Drug Deliv. 2005;3:141–54.
59. Laffleur F, Bernkop-Schnürch A. Thiomers: promising platform for macromolecular drug delivery. Future Med Chem. 2012;4(17):2205–16.
60. Anitha A, et al. Development of mucoadhesive thiolated chitosan nanoparticles for biomedical applications. Carbohyd Polym. 2011;83(1):66–73.
61. Shen J, et al. Mucoadhesive effect of thiolated PEG stearate and its modified NLC for ocular drug delivery. J Control Release. 2009;137(3):217–23.
62. Sajeesh S, et al. Thiol functionalized polymethacrylic acid-based hydrogel microparticles for oral insulin delivery. Acta Biomater. 2010;6(8):3072–80.
63. Bernkop-Schnürch A, Hornof M, Zoidl T. Thiolated polymers—thiomers: synthesis and in vitro evaluation of chitosan–2-iminothiolane conjugates. Int J Pharm. 2003;260(2):229–37.
64. Bernkop-Schnürch A. Thiomers: a new generation of mucoadhesive polymers. Adv Drug Deliv Rev. 2005;57(11):1569–82.
65. Jindal AB, Wasnik MN, Nair HA. Synthesis of thiolated alginate and evaluation of mucoadhesiveness, cytotoxicity and release retardant properties. Indian J Pharm Sci. 2010;72(6):766.
66. Marschütz MK, Bernkop-Schnürch A. Thiolated polymers: self-crosslinking properties of thiolated 450 kDa poly (acrylic acid) and their influence on mucoadhesion. Eur J Pharm Sci. 2002;15(4):387–94.
67. Sarti F, et al. Thiolated hydroxyethylcellulose: Synthesis and in vitro evaluation. Eur J Pharm Biopharm. 2010;76(3):421–7.

68. Rahmat D, et al. Design and synthesis of a novel cationic thiolated polymer. Int J Pharm. 2011;411(1–2):10–7.
69. Shen J, et al. Thiolated nanostructured lipid carriers as a potential ocular drug delivery system for cyclosporine A: Improving in vivo ocular distribution. Int J Pharm. 2010;402(1–2):248–53.
70. Makhlof A, et al. Nanoparticles of glycol chitosan and its thiolated derivative significantly improved the pulmonary delivery of calcitonin. Int J Pharm. 2010;397(1–2):92–5.
71. Hombach J, Hoyer H, Bernkop-Schnürch A. Thiolated chitosans: development and in vitro evaluation of an oral tobramycin sulphate delivery system. Eur J Pharm Sci. 2008;33(1):1–8.
72. Iqbal J, et al. Development and in vivo evaluation of an oral drug delivery system for paclitaxel. Biomaterials. 2011;32(1):170–5.
73. Hombach J, Palmberger TF, Bernkop-Schnürch A. Development and in vitro evaluation of a mucoadhesive vaginal delivery system for nystatin. J Pharm Sci. 2009;98(2):555–64.
74. Hoyer H, et al. Preparation and evaluation of microparticles from thiolated polymers via air jet milling. Eur J Pharm Biopharm. 2008;69(2):476–85.
75. Dash M, et al. Chitosan—A versatile semi-synthetic polymer in biomedical applications. Prog Polym Sci. 2011;36(8):981–1014.
76. Radhakumary C, Antonty M, Sreenivasan K. Drug loaded thermoresponsive and cytocompatible chitosan based hydrogel as a potential wound dressing. Carbohyd Polym. 2011;83(2):705–13.
77. Bernkop-Schnürch A, et al. In vitro evaluation of the potential of thiomers for the nasal administration of Leu-enkephalin. Amino Acids. 2006;30:417–23.
78. Bernkop-Schnürch A, et al. Preparation and characterisation of thiolated poly (methacrylic acid)–starch compositions. Eur J Pharm Biopharm. 2004;57(2):219–24.
79. Zambito Y, Di Colo G. Thiolated quaternary ammonium–chitosan conjugates for enhanced precorneal retention, transcorneal permeation and intraocular absorption of dexamethasone. Eur J Pharm Biopharm. 2010;75(2):194–9.
80. Baloglu E, et al. In vitro evaluation of mucoadhesive vaginal tablets of antifungal drugs prepared with thiolated polymer and development of a new dissolution technique for vaginal formulations. Chem Pharm Bull. 2011;59(8):952–8.
81. Langoth N, Kalbe J, Bernkop-Schnürch A. Development of buccal drug delivery systems based on a thiolated polymer. Int J Pharm. 2003;252(1–2):141–8.
82. Yin L, et al. Drug permeability and mucoadhesion properties of thiolated trimethyl chitosan nanoparticles in oral insulin delivery. Biomaterials. 2009;30(29):5691–700.
83. Haglund BO, Joshi R, Himmelstein KJ. An in situ gelling system for parenteral delivery. J Control Release. 1996;41(3):229–35.
84. Anumolu SS, et al. Design and evaluation of novel fast forming pilocarpine-loaded ocular hydrogels for sustained pharmacological response. J Control Release. 2009;137(2):152–9.
85. Bernkop-Schnürch A, et al. Preparation and in vitro characterization of poly (acrylic acid)–cysteine microparticles. J Control Release. 2003;93(1):29–38.
86. Lemp A. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. Eye Contact Lens. 1995;21(4):221–32.
87. Iqbal J, et al. Preactivated thiomers as mucoadhesive polymers for drug delivery. Biomaterials. 2012;33(5):1528–35.
88. Solhi L, et al. Synthesis and in vitro characterization of a preactivated thiomer via polymerization reaction. Biomacromol. 2012;13(10):3054–63.
89. Grabovac V, Guggi D, Bernkop-Schnürch A. Comparison of the mucoadhesive properties of various polymers. Adv Drug Deliv Rev. 2005;57(11):1713–23.
90. Jahan F, et al. Development of mucoadhesive thiomeric chitosan nanoparticles for the targeted ocular delivery of vancomycin against Staphylococcus aureus resistant strains. Nanofabrication. 2021;6(1):16–24.
91. Krauland AH, Hoffer MH, Bernkop-Schnürch A. Viscoelastic properties of a new in situ gelling thiolated chitosan conjugate. Drug Dev Ind Pharm. 2005;31(9):885–93.
92. Bernkop-Schnürch A, Thaler SC. Polycarbophil–cysteine conjugates as platforms for oral polypeptide delivery systems. J Pharm Sci. 2000;89(7):901–9.
93. Valenta C, et al. Evaluation of the inhibition effect of thiolated poly (acrylates) on vaginal membrane bound aminopeptidase N and release of the model drug LH-RH. J Pharm Pharmacol. 2002;54(5):603–10.
94. Szilágyi BÁ, et al. In situ gelation of thiolated poly(aspartic acid) derivatives through oxidant-free disulfide formation for ophthalmic drug delivery. Colloids Surf, B. 2023;225: 113254.
95. Hornof MD, Bernkop-Schnürch A. In vitro evaluation of the permeation enhancing effect of polycarbophil–cysteine conjugates on the cornea of rabbits. J Pharm Sci. 2002;91(12):2588–92.
96. Asim MH, et al. Thiolated cyclodextrins: Mucoadhesive and permeation enhancing excipients for ocular drug delivery. Int J Pharm. 2021;599: 120451.
97. Hugger ED, Audus KL, Borchardt RT. Effects of poly (ethylene glycol) on efflux transporter activity in Caco-2 cell monolayers. J Pharm Sci. 2002;91(9):1980–90.
98. Kabanov AV, Batrakova EV, Miller DW. Pluronic® block copolymers as modulators of drug efflux transporter activity in the blood–brain barrier. Adv Drug Deliv Rev. 2003;55(1):151–64.
99. Werle M, Hoffer M. Glutathione and thiolated chitosan inhibit multidrug resistance P-glycoprotein activity in excised small intestine. J Control Release. 2006;111(1–2):41–6.
100. Föger F, Schmitz T, Bernkop-Schnürch A. In vivo evaluation of an oral delivery system for P-gp substrates based on thiolated chitosan. Biomaterials. 2006;27(23):4250–5.
101. Bernkop-Schnürch A, Guggi D, Pinter Y. Thiolated chitosans: development and in vitro evaluation of a mucoadhesive, permeation enhancing oral drug delivery system. J Control Release. 2004;94(1):177–86.
102. Weng Y, et al. Nanotechnology-based strategies for treatment of ocular disease. Acta pharmaceutica sinica B. 2017;7(3):281–91.
103. Nwabor OF, et al. Facile deposition of biogenic silver nanoparticles on porous alumina discs, an efficient antimicrobial, antibiofilm, and antifouling strategy for functional contact surfaces. Biofouling. 2021;37(5):538–54.
104. Ontong JC, et al. Potential of antimicrobial topical gel with synthesized biogenic silver nanoparticle using Rhodomyrtus tomentosa leaf extract and silk sericin. Biotech Lett. 2020;42(12):2653–64.
105. Nagime PV, et al. Facile synthesis of silver nanoparticles using Calotropis procera leaves: unraveling biological and electrochemical potentials. Discover Nano. 2024;19(1):139.
106. Nwabor OF, et al. Enhancement of food shelf life with polyvinyl alcohol-chitosan nanocomposite films from bioactive Eucalyptus leaf extracts. Food Biosci. 2020;36: 100609.
107. Jayeoye, T.J., et al., Multifarious Biological Applications and Toxic Hg2+ Sensing Potentiality of Biogenic Silver Nanoparticles Based on Securidaca inappendiculata Hassk Stem Extract. International Journal of Nanomedicine, 2021. 16(null): p. 7557–7574.
108. Syukri DM, et al. Antibacterial-coated silk surgical sutures by ex situ deposition of silver nanoparticles synthesized with Eucalyptus camaldulensis eradicates infections. J Microbiol Methods. 2020;174: 105955.
109. Vélez E, et al. Silver Nanoparticles Obtained by Aqueous or Ethanolic Aloe vera Extracts: An Assessment of the Antibacterial Activity and Mercury Removal Capability. J Nanomater. 2018;2018(1):7215210.
110. Jayeoye TJ, et al. Green synthesis of silver nanoparticles using cytocompatible polymer derivative of tara gum for gold (III) ion detection in water samples. J Polym Environ. 2024;32: 6667–86.
111. Nagime PV, et al. Biogenic Fabrication of Silver Nanoparticles Using Calotropis procera Flower Extract with Enhanced Biomimetics Attributes. Materials. 2023;16(11):4058.
112. Nagime PV, Syukri DM, Sjahriani T, Hermawan D, Shaikh NM, Shafi S, Chidrawar VR, Singh S, Kausar N, Elamin A. Phyto-mediated biosynthesis of silver nanoparticles using Aloe barbadensis Miller leaves gel with improved antibacterial, anti-fungal, antioxidant, anti-inflammatory, anti-diabetic, and anti-cancer activities. Nano-Structures Nano-Objects. 2024;40:101368.
113. Syukri DM, et al. Prevention of post-operative bacterial colonization on mice buccal mucosa using biogenic silver nanoparticles-coated nylon sutures. Regen Eng Transl Med. 2024;10:294–308.
114. Nwabor OF, et al. Valorization of Wastepaper Through Antimicrobial Functionalization with Biogenic Silver Nanoparticles, a Sustainable Packaging Composite. Waste and Biomass Valorization. 2021;12(6):3287–301.

115. Mohite P, et al. Lipid-based oral formulation in capsules to improve the delivery of poorly water-soluble drugs. Front Drug Delivery. 2023;3:1232012.
116. Patel P, et al. Lipid Nanoparticulate Drug Delivery Systems: Approaches toward Improvement in Therapeutic Efficacy of Bioactive Molecules: Pharmaceuticals. 2024;17(3):329.
117. Shah S, et al. Lipids fortified nano phytopharmaceuticals: A breakthrough approach in delivering bio-actives for improved therapeutic efficacy. Pharm Nanotech. 2024;13(1):70–89.
118. Vyas J, et al. Sustainable sources of raw materials as substituting biomaterials for additive manufacturing of dental implants: a review. Periodontal and Implant Research. 2024;8(1):3.
119. Van der Lubben IM, et al. Chitosan microparticles for oral vaccination: preparation, characterization and preliminary in vivo uptake studies in murine Peyer's patches. Biomaterials. 2001;22(7):687–94.
120. Zhu X, et al. Synthesis of thiolated chitosan and preparation nanoparticles with sodium alginate for ocular drug delivery. Mol Vis. 2012;18:1973.
121. Vyas J, et al. Potential Applications and Additive Manufacturing Technology-Based Considerations of Mesoporous Silica: A Review. AAPS PharmSciTech. 2023;25(1):6.
122. Li J, Mooney DJ. Designing hydrogels for controlled drug delivery. Nat Rev Mater. 2016;1(12):1–17.
123. Shu XZ, et al. Disulfide cross-linked hyaluronan hydrogels. Biomacromol. 2002;3(6):1304–11.
124. Shu XZ, et al. Disulfide-crosslinked hyaluronan-gelatin hydrogel films: a covalent mimic of the extracellular matrix for in vitro cell growth. Biomaterials. 2003;24(21):3825–34.
125. Jin R, et al. Synthesis and characterization of hyaluronic acid–poly (ethylene glycol) hydrogels via Michael addition: An injectable biomaterial for cartilage repair. Acta Biomater. 2010;6(6):1968–77.
126. Zarembinski TI, et al. Thiolated hyaluronan-based hydrogels crosslinked using oxidized glutathione: An injectable matrix designed for ophthalmic applications. Acta Biomater. 2014;10(1):94–103.
127. Wirostko B, et al. Ophthalmic uses of a thiol-modified hyaluronan-based hydrogel. Adv Wound Care. 2014;3(11):708–16.
128. Arslan M, et al. Fabrication of poly (ethylene glycol)-based cyclodextrin containing hydrogels via thiol-ene click reaction. Eur Polymer J. 2015;62:426–34.
129. Kast CE, Bernkop-Schnürch A. Thiolated polymers—thiomers: development and in vitro evaluation of chitosan–thioglycolic acid conjugates. Biomaterials. 2001;22(17):2345–52.
130. Souza JG, et al. Transcorneal iontophoresis of dendrimers: PAMAM corneal penetration and dexamethasone delivery. J Control Release. 2015;200:115–24.
131. Ge X, et al. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics. 2019;11(2):55.
132. Lu H, et al. A review on polymer and lipid-based nanocarriers and its application to nano-pharmaceutical and food-based systems. Front Nutr. 2021;8: 783831.
133. Dünnhaupt S, et al. S-protected thiolated chitosan for oral delivery of hydrophilic macromolecules: evaluation of permeation enhancing and efflux pump inhibitory properties. Mol Pharm. 2012;9(5):1331–41.
134. Bhargav E. Thiomers fresh drift of polymers & their prospective in pharmaceuticals: A review. World J Pharmacy Pharm Sci. 2013;3(1):204–20.
135. Khanuja HK, et al. Nanosuspensions-An Update on Recent Patents, Methods of Preparation, and Evaluation Parameters. Recent Pat Nanotechnol. 2021;15(4):351–66.
136. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomaterials research. 2020;24(1):3.
137. Shi S, et al. Chitosan grafted methoxy poly (ethylene glycol)-poly (ε-caprolactone) nanosuspension for ocular delivery of hydrophobic diclofenac. Sci Rep. 2015;5(1):11337.
138. Josyula A, et al. An ion-paired moxifloxacin nanosuspension eye drop provides improved prevention and treatment of ocular infection. Bioengineering & Translational Medicine. 2021;6(3): e10238.
139. Qin T, et al. Nanosuspension as an efficient carrier for improved ocular permeation of voriconazole. Curr Pharm Biotechnol. 2021;22(2):245–53.
140. Ghosh PK, Murthy RSR. Microemulsions: a potential drug delivery system. Curr Drug Deliv. 2006;3(2):167–80.
141. Seng, K.K. and W.V. Loong, Introductory chapter: From microemulsions to nanoemulsions. Nanoemulsions-Properties, Fabrications and Applications, 2019.
142. Gawin-Mikołajewicz A, et al. Ophthalmic nanoemulsions: From composition to technological processes and quality control. Mol Pharm. 2021;18(10):3719–40.
143. Akhter S, et al. Improving the topical ocular pharmacokinetics of an immunosuppressant agent with mucoadhesive nanoemulsions: Formulation development, in-vitro and in-vivo studies. Colloids Surf, B. 2016;148:19–29.
144. Ohta Y, et al. Preventive effect of vitamin E-containing liposome instillation on cataract progression in 12-month-old rats fed a 25% galactose diet. J Ocul Pharmacol Ther. 2000;16(4):323–35.
145. Liao Y-T, et al. Gelatin-functionalized mesoporous silica nanoparticles with sustained release properties for intracameral pharmacotherapy of glaucoma. Journal of Materials Chemistry B. 2017;5(34):7008–13.
146. Natarajan JV, et al. Sustained drug release in nanomedicine: a long-acting nanocarrier-based formulation for glaucoma. ACS Nano. 2014;8(1):419–29.
147. Schwartz SG, et al. Drug delivery techniques for treating age-related macular degeneration. Expert Opin Drug Deliv. 2014;11(1):61–8.
148. Wong CW, Wong TT. Posterior segment drug delivery for the treatment of exudative age-related macular degeneration and diabetic macular oedema. Br J Ophthalmol. 2019;103(10):1356–60.
149. Tavakoli S, et al. Liposomal sunitinib for ocular drug delivery: A potential treatment for choroidal neovascularization. Int J Pharm. 2022;620: 121725.
150. Fangueiro JF, et al. Current nanotechnology approaches for the treatment and management of diabetic retinopathy. Eur J Pharm Biopharm. 2015;95:307–22.
151. Pietruszyńska M, et al. Ophthalmic manifestations of atopic dermatitis. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii. 2020;37(2):174–9.
152. Sufian MA, et al. Moxifloxacin-loaded nanoparticles of thiolated xyloglucan for ocular drug delivery: Permeation, mucoadhesion and pharmacokinetic evaluation. Int J Biol Macromol. 2024;270: 132522.
153. Liu D, et al. Ex Vivo and in Vivo evaluation of the effect of coating a coumarin-6-labeled nanostructured lipid carrier with chitosan-N-acetylcysteine on rabbit ocular distribution. Mol Pharm. 2017;14(8):2639–48.
154. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev. 2005;57(11):1595–639.
155. Hornof M, et al. Mucoadhesive ocular insert based on thiolated poly (acrylic acid): development and in vivo evaluation in humans. J Control Release. 2003;89(3):419–28.
156. Hoeller S, et al. Safety and tolerability of chitosan-n-acetylcysteine eye drops in healthy young volunteers. Invest Ophthalmol Vis Sci. 2011;52(14):3841–3841.
157. Durrie DS, et al. Ability of a new crosslinked polymer ocular bandage gel to accelerate reepithelialization after photorefractive keratectomy. J Cataract Refract Surg. 2018;44(3):369–75.
158. Lee H, Noh H. Advancements in Nanogels for Enhanced Ocular Drug Delivery: Cutting-Edge Strategies to Overcome Eye Barriers. Gels. 2023;9(9):718.
159. Goostrey, T., Preactivated Thiomer Mucoadhesive Micelles for Anterior Ophthalmic Drug Delivery. 2021.
160. Mahapatra I, et al. Expert perspectives on potential environmental risks from nanomedicines and adequacy of the current guideline on environmental risk assessment. Environ Sci Nano. 2018;5(8):1873–89.
161. Foulkes R, et al. The regulation of nanomaterials and nanomedicines for clinical application: Current and future perspectives. Biomaterials science. 2020;8(17):4653–64.
162. Cuine, J., et al., Mucoadhesive ocular delivery system for the treatment of glaucoma. 2024, Google Patents.

Publisher's Note